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Annals of Surgery
December 1944

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EXPERIENCES WITH BATTLE WOUNDS OF THE HEAD

COLONEL R A MONEY A A M C, AND LT COL T Y NELSON, A A M C

FROM A NEUROSURGICAL CENTER AT AN AUSTRALIAN GENERAL HOSPITAL IN THE MIDDLE EAST

THE SURGERY OF BATTLE CASUALTIES is largely concerned with the care of infected wounds and compound fractures. The general principles applicable to these injuries hold good for all regions of the body, but wounds of the head present special problems owing to certain anatomic and physiologic peculiarities of the structures involved in the scalp, skull, meninges and brain.

In the case of the scalp and skull, their liberal blood supply gives them increased resistance against virulent infections, especially those due to anaerobes, and massive necrosis and gangrene are extremely rare. On the other hand, their intricate lymphatic and venous connections through the osseous diploe, and from the brain and meninges make the persistence of apparently minor and latent sepsis in the scalp a menace likely to result in unsuspected and deeper infections at some later date.

The arrangement of the outer and inner tables in the bones of the cranial vault allows even a small missile to cause much more damage to the inner table than the outer, or than would be suspected from a superficial examination of the wound. In this connection, it is most important to realize the terrific kinetic energy ($\frac{1}{2}mv^2$) of a missile of small mass (m) owing to its high velocity (v) at the moment of impact.

The protective barrier-like function of the dura mater is well known and every effort must be made to conserve it. Indeed, the whole prognosis of head wounds depends on whether or not it has been penetrated either by the missile itself or by pieces of indriven bone or hat. Somewhat unexpectedly, and contrary to the experience of the Great War of 1914-1918, it has been found in this series of cases that pieces of metal from bombs, shells, *etc.*, are, in themselves, relatively innocuous inside the skull, due to the fact that the earth and sand of the desert have not been manured and contain comparatively few virulent organisms, and the missiles are almost red-hot when they enter. In fact, Major P B Ascroft, R A M C, of another Neurosurgical Unit in the Middle East, relates how an officer patient severely burned his thumb and index finger trying to pull out a small piece of bomb splinter after it had penetrated his steel helmet and just stuck in his frontal bone, without causing any loss of consciousness! On the other hand, organic foreign bodies such as pieces of indriven bone felt and sponge rubber from hats and steel helmets seem to form a nidus

for bacteria and are always a potential source of danger until removed. Failure to recognize their presence, especially after comparatively minor injuries, has occurred during the rush of casualties, and almost invariably serious and even fatal consequences have resulted, as will be shown later. Thus, the practice of always removing organic foreign bodies has been adopted. Inorganic foreign bodies alone have been left *in situ* if not readily accessible and provided the presence of abscess or other space-consuming lesion has been excluded by an examination of the cerebrospinal fluid, and by encephalography. It is as yet too early to tell whether their retention will be more conducive to posttraumatic epilepsy than the gliosis and scar which must remain, even after their removal.

Finally, the management of wounds of the head is not a mere exercise in operative technic, even granted that adequate facilities are available. A careful neurologic examination, to determine the extent of the underlying damage to the brain (if any) must be made as early as possible, if useless and unnecessary operations are to be avoided, and if true significance is to be attached to any alteration in clinical signs which may be observed later. It must always be borne in mind that the damage done to the brain at the time of injury is irreparable, except by Nature's methods, and that operations should only be undertaken for the prevention of sepsis and the relief of compression by depressed bone, hemorrhage, or abscess. The clinical condition of the patient, varying from time to time, may be the only guide as to whether to open the dura mater or not, a most important decision to arrive at, in view of its protective function already mentioned. The method of recording these early and subsequent essential observations is shown in Figures 1 and 2 (Head Injury Card). Remember that evidence of local or focal cerebral damage, as manifested by aphasia, monoplegia, hemiplegia, visual field defects and other neurologic syndromes, is not, in itself, an indication for operation in the early stages after wounding. Such signs are common, especially after tangential nonpenetrating wounds, which may not even injure the skull. Increasing depth of unconsciousness is the cardinal sign of compression calling for urgent operative measures, and in the absence of this sign and foreign bodies (mainly bone fragments), intracranial surgical procedures should be deferred.

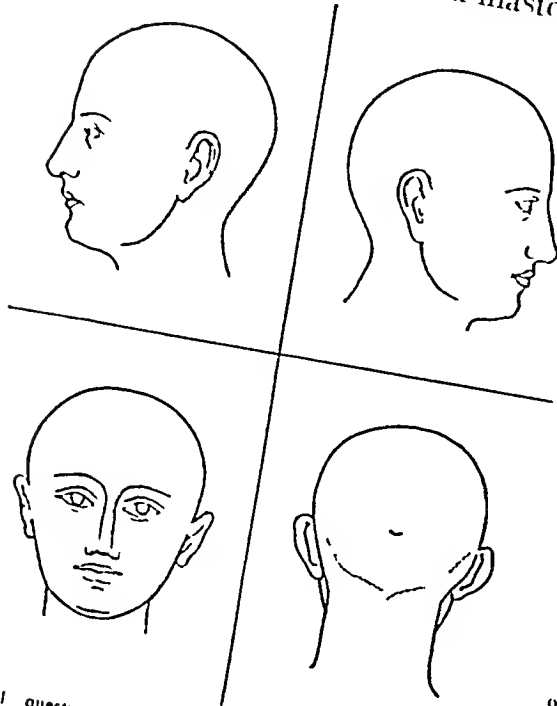
CLASSIFICATION AND TERMINOLOGY

A total number of 78 cases of all types were treated at this Center between July and December, 1942, during the fighting in the vicinity of El Alamein. In 25 of these cases there had been penetration of the dura mater. A review of this material indicated that open wounds of the head could be classified into the following six groups (modified from Cushing's nomenclature)

- 1 Scalp wounds
- 2 Wounds of the skull, without depression of fragments
- 3 Wounds of the skull, with depression of fragments but without penetration of the dura

BATTLE WOUNDS OF HEAD

- 4 Wounds of the skull and brain with penetration of the dura
- 5 Perforating, or "through-and-through" wounds
- 6 Penetrating or perforating wounds through the orbits, accessory nasal sinuses and mastoid an cells



Army Form W 3115a

HEAD INJURY CARD

For use in Field Ambulances, Casualty Clearing Stations and all Hospitals

At each Station or Hospital a new card must be filled in and placed with the other cards in the patient's envelope — A I W 3115a

NAME _____ NO _____
(BLOCK CAPITALS)

Rank _____ Unit _____

Date and time of injury _____

Date and time of examination _____

External injury? _____ If fracture seen? _____

Injured? _____ Depressed? _____

(Site of external wounds to be marked on diagrams on back of this card)

L2 O H Q P / 10 000/12-41

All questions marked with interrogation mark to be answered with — + = Yes
O = No

MENTAL STATE

Alert? _____ Drowsy? _____ Comatose? _____

Lucid? _____ Confused? _____

Quiet? _____ Excited? _____

Irritable? _____

PUPILS

Dilated? _____ Pin point? _____ Equal? _____

R. Larger? _____ L. Larger? _____

WEAKNESS OR PARALYSIS?

R. Lt limbs? _____ Left Limbs? _____

PULSE RATE? _____ Fits? _____

RESPIRATION RATE _____

TREATMENT GIVEN

Morphine given? _____ Dose _____

Sulphonamide given? _____

A.T.S. given? _____

PROGRESS UNDER OBSERVATION

Improved? _____ Stationary? _____ Worse? _____

REMARKS —

FIG 1 and 2—Head Injury Card, showing four sides

Signature of M.O.

Wounds in Groups 3, 4, 5 and 6 should be regarded as severe Wounds caused by bullets from revolvers, rifles, light automatic weapons ("tommy-guns") and machine guns (all types) were called "gunshot wounds," or "G S W"

Wounds caused by splinters or fragments of metal from field-gun and antitank shells aerial bombs, mortars, land-mines and "booby" traps were called "shrapnel wounds," or "S W"

Wounds having only a site of entry for the foreign body which was retained were called "penetrating"

Wounds having both sites of entry and exit were called "perforating"

Many patients had received more than one wound of the head, and often of different types, and others had received in addition, wounds of other regions, of greater or lesser severity. The presence of "multiple" wounds and their complications must always be borne in mind when interpreting a patient's clinical condition in its true perspective.

TIME AND PLACE FOR TREATMENT

If a soldier with a wound of the head is unable to survive the first 12 hours, it is unlikely that he will live irrespective of what is done for him; thus, except in the case of meningeal hemorrhage or rapidly spreading subdural hematoma or severe arterial hemorrhage from the scalp, urgent surgical interference is rarely necessary. Adequate facilities and essential instruments, especially an electrosurgical unit and some form of suction apparatus, as well as a portable roentgenologic unit are necessary for dealing correctly with wounds of the head, especially those which involve the dura mater or deeper structures. Even if the medical officer dealing with them is not a fully trained neurosurgeon, he should at least be familiar with the technics employed in the care of damaged brain and in the control of intracranial bleeding, by the use of bulb syringes and warm saline, suction, silver clips, electrosurgery and muscle "stamps." He should also have a skilled assistant and anesthetist. These postulates have rarely been found at field ambulance dressing stations, even with attached field surgical units, or at casualty clearing stations under existing conditions, and with the number of medical personnel available up to the present.

Furthermore, apart from scalp and superficial skull toilet, hasty and often incomplete operations are best avoided, especially when the patient cannot be "held" for some days after the operation, for it has been proved frequently that although patients with severe head wounds stand transportation well before operation, they travel badly afterwards. Finally, it has been shown repeatedly that the time factor is not as important in dealing with head wounds as with wounds in other regions where the ideal time limit is set at 12 hours, or even less for abdominal wounds. This longer period of safety for head wounds had been fixed at 48 hours for civilian casualties during bombing raids on Great Britain in 1940-41, but in wounds from the Western Desert, for reasons already stated, successful excision, toilet, and closure with a short period of drainage has been accomplished, frequently as late as 72 hours after wounding and in the following case, a period of ten days elapsed before adequate surgical attention was given.

Case 1—Pvt R S G, age 22, was wounded in the head on October 26, 1942 when a land-mine exploded near him. He did not lose consciousness but complained of some transient numbness of the left hand. He received extensive lacerated wounds of the scalp, in the right parietal region, with a hanging flap exposing much bone.

BATTLE WOUNDS OF HEAD

There were also numerous other smaller scalp wounds nearby, posteriorly and towards the vertex. At a main dressing station, sulphanilamide powder and vaselined gauze were applied and he was hastily evacuated to an Australian general hospital about 90 miles in the rear, where he arrived early on October 27. Owing to the rush of casualties here, no operation was performed although roentgenograms taken that day showed a metal fragment of moderate size embedded in the skull just to the right of the vertex, with a small depressed fragment of bone indriven ahead of it. There were also several smaller extracranial fragments further posteriorly and laterally (Fig 3). The wounds were dressed on several occasions, sulphonamides were continued by mouth and he was evacuated by ambulance train to this Center, where he arrived late in the evening of November 3, 1942.



FIG 3—Case 1. Anteroposterior view, showing the irregularly shaped metallic foreign body in the skull, near vertex, and to the right of the midline.

On examination, the patient looked ill. There was a foul smelling discharge from the extensive scalp wound. A portion of the loose scalp flap was necrotic, and much debris, dirt and hair could still be seen under its edges. The large foreign body was felt in a separate and smaller wound about three centimeters away. It was not so septic, and neither were the remaining small scalp wounds. At operation next day, under anesthesia with pentothal sodium given intravenously, the largest foreign body and small piece of indriven bone were removed with difficulty. The dura mater was intact and, after excision of the edges, this wound was sutured, without drainage. In a similar manner, the other small wounds were excised and closed. The large dirty wound was thoroughly washed out, all debris carefully removed, necrotic areas

of scalp excised down to the pericranium, and careful hemostasis secured. The fresh edges of the wound could only be partly approximated with silkworm gut sutures, leaving exposed an area of pericranium, about 3 x 2 cm. Complete closure was impossible owing to loss of scalp tissue, and, relieving incisions in the scalp being abhorred, a dressing of sulphanilamide powder and vaselined gauze was applied. This dressing was not disturbed for six days, and when removed, despite the onset of infective hepatitis on November 5, which had necessitated the suspension of sulphapyridine therapy by mouth, the closed wounds had healed and the raw area was covered with clean granulations. Secondary suture of this area was successfully accomplished by an undermining plastic procedure about three weeks later, when the jaundice had cleared up. He was discharged, with all wounds healed, to a convalescent depot on December 12, 1942, five weeks after arrival at this Center.

From the foregoing desiderata and statistics supplied personally by Major P. B. Ascroft, R.A.M.C., it has been shown in the treatment of head wounds that the best results were obtained by transporting all patients with other than minor head wounds back to some Special Center, (equipped and prepared to deal with and hold this class of case) preferably by aeroplane, as was done almost exclusively after the break-through by the Eighth British Army at El Alamein and by the Germans in their campaigns, even if it involved a delay of 72 hours, or more, until surgical measures were instituted. Having special Neurologic Centers in the forward areas was tried during the earlier desert campaigns, but was not found to be of much practical use at that time, owing to the difficulty of collecting and segregating head cases in forward areas and the lack of "holding" facilities.

THE OBJECTS OF TREATMENT

The objects to be aimed at in the treatment of head wounds are

- (1) To restore the injured structures as nearly as possible to normal, by the removal of destroyed tissues and of foreign bodies as soon as possible
- (2) To prevent complications which may lead to disability, deformity or death, by converting open wounds into closed, clean ones, when feasible
- (3) To return the soldier to his unit, in the shortest possible time, without the necessity of down-grading

The complete attainment of these ideals is rarely practicable with battle casualties even at Special Centers, as will be realized from a consideration of the difficulties met with in this series.

GENERAL PROCEDURES AT SPECIAL CENTERS

Owing to its situation at the Base, and the long time taken for evacuation by ambulance trains and sometimes also by hospital ships, most of the patients in this series did not reach this Center until infection was already active, or else their wounds were healing. However, as a result of experience gained in the management of these wounds, mainly in their late stages, and from observations made at other Neurosurgical Centers, where the injuries were dealt with in a more recent state, a plan of treatment was evolved which proved effective for the conditions found in Middle East. A short description of the procedures advocated will now be given, followed by case

reports, selected to illustrate some of the complications and difficulties encountered.

As soon as the patient has been fed and rested after his journey, the hair is clipped short with fine cutting clippers all over the scalp, if not already done. This was found to be a most necessary step in order to remove all dirt and old blood, and to enable a careful inspection of the head to be made. Frequently the hair had only been hastily cut from the vicinity of the main wound and other smaller wounds had not been recognized.

Dressings are then inspected and the plan of treatment decided upon. Here, as at all subsequent dressings and inspections, every person present must wear an adequate surgical mask, covering the nose as well as the mouth. The "no-touch" (except with dressing forceps) technic of doing dressings must be adopted from the start, in order to reduce cross-infections to a minimum. As a guide for the future, if the wound is already infected and discharging, a swabbing is taken and an immediate smear and culture is made, to determine the predominating organisms (if any). Where sulphonamides had already been given in adequate dosage, cultures were frequently sterile. Complete and differential blood counts are also advisable to exclude anemia and postsulphonamide leukopenia. If satisfactory roentgenograms do not arrive with the patient, he is then sent to the Department of Radiology, with a request for anteroposterior, lateral and, occasionally, tangential exposures. Where indriven bone fragments and retained foreign bodies are suspected or found, stereoscopic views, taken with a Potter-Bucky diaphragm or Lysholm grid, are extremely helpful before attempting their removal. The importance of radiologic examinations of *all* battle wounds of the head, however slight, and even if consciousness has not been lost, has already been mentioned, and the mistakes which will otherwise be made, will be referred to again later.

If operation is decided upon, the whole head is then closely and carefully shaved by a *skilled* orderly with a *sharp* razor (both difficult to obtain and retain in the Army!). This is a very important step in eliminating infections and in enabling the postoperative and subsequent dressings to be adequately retained in place with a minimum of adhesive plaster. The scalp is painted with a 2% aqueous solution of iodine, after scrubbing with ethereal soap. If infection has not already developed in the scalp beyond the edges of the wound, local anesthesia, by the method of regional block, can be used with 1% ethocaine and adrenalin 1,200,000, in physiologic saline solution, after premedication with alopon (omnupon) gr $\frac{1}{3}$ and scopolamine gr $\frac{1}{150}$, given hypodermically an hour and a half beforehand. The alopon can be repeated half an hour before operation if necessary. In the presence of established infection in scalp or bone, or with a noncooperative nervous patient, general anesthesia is preferable by the administration of pentothal sodium intravenously, in 5% solution for induction and in weaker solution in saline or glucose-saline for maintenance. Fluids or blood should

be given intravenously during operation if the patient is dehydrated or anemic. In cases already infected and where streptococci, pneumococci, Friedlander's bacilli or anaerobes predominate, an initial dose of four grams of sulphadiazine is given by mouth, or, if the patient is unable to swallow or has meningitis, three Gm is given intravenously in a 30% solution. If the predominating organism is a staphylococcus, it is felt that a similar dose of sulphathiazole has more effect and less risk of producing complications. During the whole of the period under review, sulphadiazine was not always obtainable and then sulphapyridine had to be used, but the former drug was found to possess many advantages over the latter, due to its much lower toxicity and the greater concentration obtainable in the cerebrospinal fluid.

WOUNDS OF THE SCALP AND SKULL, WITHOUT DEPRESSION (GROUPS 1 AND 2)

In these groups some of the most serious and prolonged cases of morbidity were encountered, chiefly because, at the time of wounding, consciousness was not lost, and they were evacuated from the regimental aid post as "walking wounded, not serious," with just a first field dressing hastily applied. At the forward dressing stations and field surgical units, even frequently at casualty clearing stations in rush periods, there was no time to attend to them when more serious cases were waiting, and upon reaching a general hospital, as the wound was by now probably more than 36 hours old, proper excision and toilet were not carried out, under the mistaken idea that too much time had elapsed. In other instances, these wounds were received along with multiple wounds of a more serious nature and were given but scanty consideration until the appearance of sepsis called for more active measures.

Furthermore, it was often found necessary to "empty-out" general hospitals, close to the battle zone, in expectation of more casualties and naturally, these cases were amongst the first to be transferred to other hospitals further back or even to convalescent depots "for dressings." Rarely had any roentgenologic examination been carried out, until some complication had occurred and only then was some osseous lesion with or without osteomyelitis detected. Two instructive cases of this group are presented.

Case 2—Pvt F G, age 26, was wounded, July 16, 1942, in the left parietal region when a bomb exploded. He never lost consciousness. The wound was dressed at an advanced dressing station four hours later, and he was passed on to a general hospital, where the dressing was changed but the wound was not excised or explored although roentgenologic examination, July 18, showed that a piece of bone had been removed from the outer table of the skull in the left parietal region near the midline. Several foreign bodies were seen in the vicinity but no fracture through the inner table was detected.

On July 28, the wound was reported "clean and healing" and he was evacuated to this Center on July 30. The wound was then healing by granulation and, with the assistance of eusol dressings, it had healed by August 8, and he was able to rejoin his training unit on August 20, 1942.

Soon afterwards the wound began to discharge. He was treated by his regimental medical officer until September 27 when he was referred to this Center com-

BATTLE WOUNDS OF HEAD

planning of severe left-sided headache. A discharging wound was present in the left parietal area, near the vertex. Two days later the surrounding scalp became indurated and edematous like a "Pott's puffy tumor." There were some swollen and tender lymphatic nodes in the left posterior triangle of the neck. Temperature 102° F. Without waiting for roentgenologic examination, he was operated upon, and a crucial incision was made to include the unhealed wound. The pericranium was raised up by pus from the underlying bare bone. Two bur holes were made in this bare area but no evidence of infection was found in the diploe or extradurally. No foreign bodies were encountered. After insufflation of sulphanilamide powder the wound was packed widely open with vaselined gauze, and sulphapyridine was administered by mouth in full dosage.

Although no further serious symptoms or complications occurred, healing by second intention took place very slowly and secondary suture never became practicable. A further roentgenologic examination made November 3 showed a trans-radiant area, close to the left parietal eminence, involving both tables of the bone, but not showing any evidence of active periostitis or osteomyelitis. One small foreign body was still present outside the skull.

He was last seen on December 14, when the wound had only just healed, but the scar was depressed, tender and adherent to the bone, and he was referred to a convalescent depot, for plastic operation later, if no further discharge occurred from the wound during the next two months.

Case 3—Corp K. M., age 37, was hit on the back of the head by a piece of falling rock from an explosion on April 17, 1942. He was only unconscious for a few minutes and was treated for a lacerated wound of the scalp "down to the bone" in the left occipital area at a field ambulance. He was later transferred to an Australian casualty clearing station where, infection occurring in the wound, a roentgenologic examination of the skull was made, but no osseous lesion detected.

A few days later, he complained of very severe headache and facial neuralgia on the left side. He arrived at this hospital on April 27 with a dirty infected wound in the left occipital area discharging freely. The surrounding scalp was tender and swollen but there was no "puffy tumor."

Hot fomentations were applied frequently, but although the wound seemed to get cleaner the headache and neuralgia became worse, with severe exacerbations, and the ocular fundi showed early papilledema. On May 8, a further roentgenologic examination showed an area of osteomyelitis near the lambdoid suture, with the presence of sequestra at the site of an old fracture. Operation was proceeded with at once. The scalp wound was excised and an area of necrotic bone with sequestra removed. An extradural abscess with thick pus was curetted off the underlying dura. The wound was sprayed with sulphanilamide powder, packed open with vaselined gauze and sulphanilamide administered by mouth in full dosage. Healing proceeded very slowly and on July 7, it became necessary to remove further sequestra from the upper edge of the gap in the bone. This produced more headache and a severe reaction in the surrounding scalp. Sulphadiazine had just been received and was now given in full dosage with such good effect that the wound had healed by August 28, when he was returned to his unit symptom-free.

Many other cases were encountered where minor sepsis occurred in scalp wounds and delayed the patient's return to his unit for much longer than would have been necessary if healing had taken place promptly. An attempt should always be made, with these groups of wounds, to secure primary healing by a complete, yet not too extensive, excision of the wound and thorough mechanical cleansing of the damaged area. After spraying with sulphanilamide powder, the galea and skin should then be closed.

separately by a double row of silk or linen thread sutures, around a small piece or pieces of corrugated rubber, for drainage. If the galea cannot be defined readily for suturing, one row of vertical mattress sutures may be employed instead.

If the edges of wound can not be drawn together without tension, even after triradiate extensions and undermining have been carried out, they should only be drawn together where possible, and the rest of the wound left open and packed with vaselined gauze, for plastic operation and secondary suture later. This procedure gives better results than attempting to obtain primary closure by making lateral relieving incisions and "sliding" the intermediate portions of the scalp across the defect.

Once sepsis had started, or if the wound broke down, then frequent applications of warm moist pads soaked in normal saline or eusol, until *complete* healing had occurred, were found most satisfactory. Any other methods, especially those which allowed a scab to form, under which pus could deceptively collect, only prolonged healing. Keeping the hairs close shaved right up to the edge of the wound was most essential.

The possibility of focal damage, often serious and permanent, being inflicted on the brain in these wounds, must always be borne in mind, especially where the impact has fallen tangentially. Such damage is usually the result of contusion and/or laceration of the brain, and does not call for exploration, unless signs of compression or massive hemorrhage are present too. The following case, in contrast with Cases 2 and 3, illustrates how rapidly scalp healing can occur, if correct, early treatment be given, and also what serious cerebral damage may underlie a superficial wound.

Case 4—Pvt R S, age 22, was wounded in the occipital region on July 11, 1942, by a splinter from a shell while wearing his steel helmet and sitting in a slit-trench. After a short period of unconsciousness, he remembered being carried away in an ambulance. At the regimental aid post, he was conscious, his wound was dressed, and he was evacuated direct to a general hospital, where he arrived 12 hours later. Here, a badly lacerated wound of the occipital region was excised, dusted with sulphamilamide powder, and sutured around a glove drain. No injury to the skull was detected at the time, nor at a roentgenologic examination made some days later.

On July 19, although the wound appeared to be healing satisfactorily, he became drowsy and restless alternately. Spinal puncture was performed and blood-stained xanthochromic cerebrospinal fluid, probably from a cerebral laceration, ran out at an initial pressure of 240 mm. The next day he was less drowsy and complained of deafness and defective vision. Examination of his fields of vision then revealed a right-sided hemianopia. On August 14, he was transferred to this Center. The wound in the scalp had healed completely but he still complained of visual difficulties although his hearing was normal. Careful estimation of his fields of vision on the Bjerrum screen now showed bilateral lower nasal and temporal quadrantic defects, *ie*, he had a false horizon just below macular vision in each eye, (Fig 4 a and b). Further investigations did not reveal the existence of any pressure effects from any space-consuming lesions and the cerebrospinal fluid was now clear. He was sent to a convalescent depot but when reexamined, October 15, the defects in the fields of vision were unaltered and down-grading became necessary.

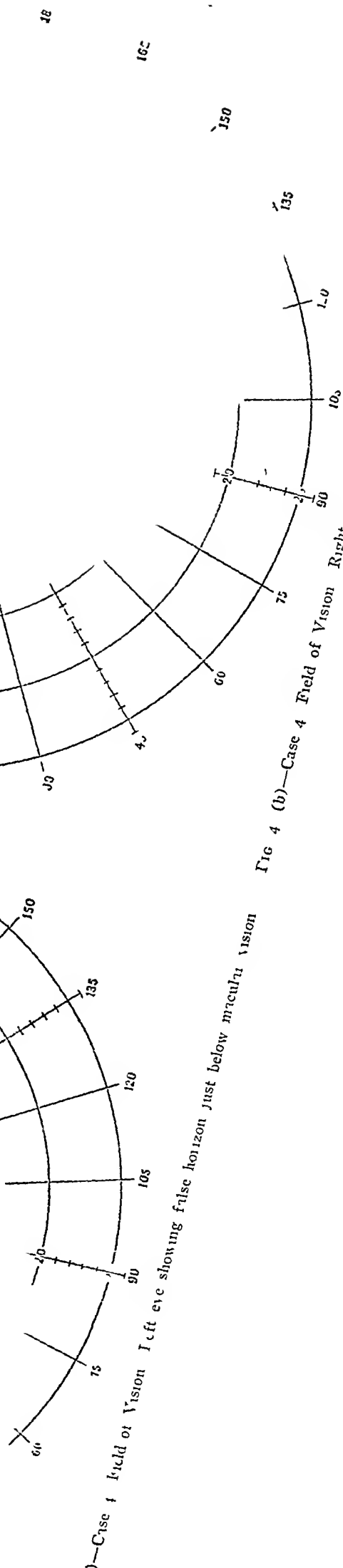
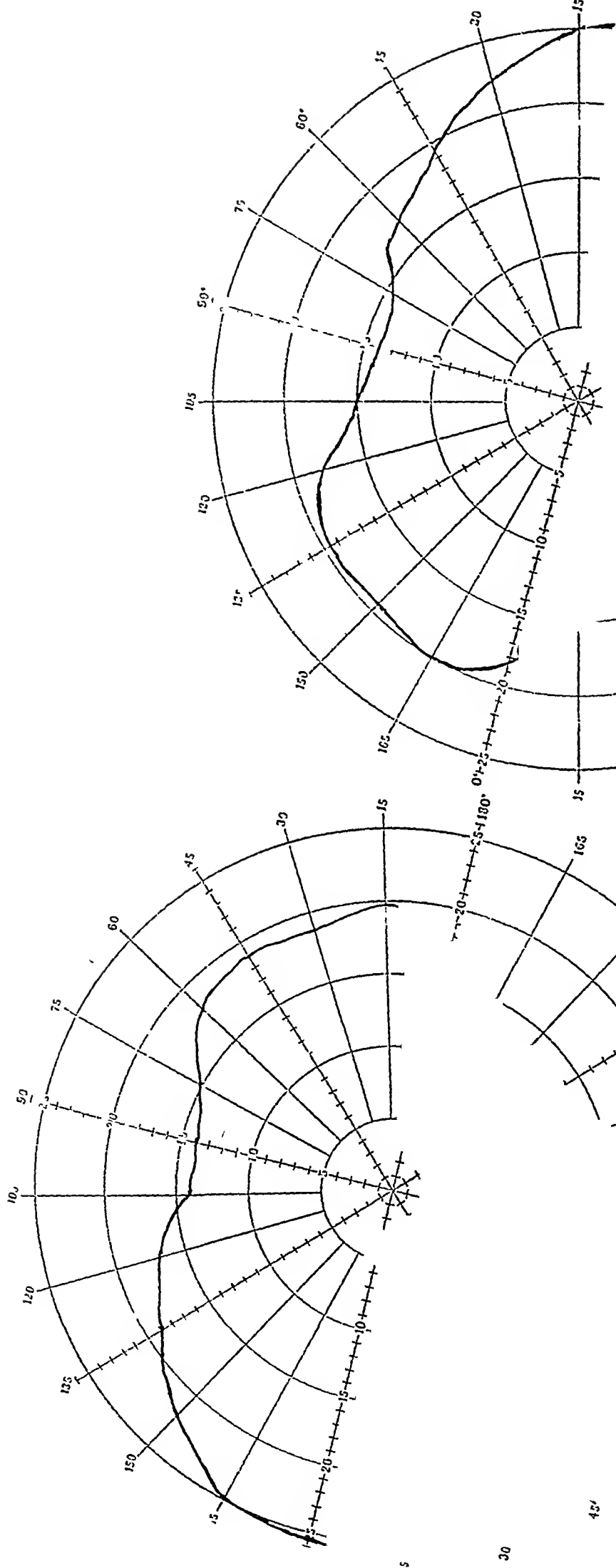


FIG 4 (a)—Case 4 Field of Vision Left eye showing false horizon just below macular vision

FIG 4 (b)—Case 4 Field of Vision Right eye showing false horizon just below macular vision

WOUNDS OF THE SKULL WITH DEPRESSION BUT WITHOUT PENETRATION OF
THE DURA (GROUP 3)

This group of wounds did not, as a rule, present any special problems. Included in it were cases of compound fissured fractures. In most instances there was more extensive involvement of the inner table than the outer table of the affected bone. The extent of these wounds was generally recognized at the first examination, consciousness had usually been lost for varying periods of time, and, being classified as severe, more attention was paid to them in the forward areas.

Careful surgical toilet and treatment, as early as possible, are necessary, however, if good results are to be obtained. Fissured fractures are rare but need thorough inspection for small retained foreign bodies, hairs and dirt between their edges and under the scalp. As in cases of Group 2, they may have areas of local brain damage deep to them, with focal neurologic signs. They do not warrant extensive craniotomy but it is often advisable to make a burr hole in the line of the fissure to exclude extra- and subdural hemorrhage.

All loose and comminuted depressed fragments should be removed, and in most cases dirt, hair and debris are found to be associated with them. Special care is necessary in the removal of depressed fragments of bone near the midline, where the longitudinal sinus might be involved, and muscle "stamps" should always be prepared in readiness for the control of sinus bleeding during their removal. But it is remarkable how deeply fragments can be depressed, without penetrating the dura. Failure to recognize and adequately treat these cases was followed, however, by long periods of disablement and serious complications, as can be seen from the following case histories.

Case 5—Lance Corp G R J, age 22, of the Royal Tank Regt received multiple "S W's" of the head when a shell exploded as he opened the front of his tank on July 17, 1942. Loss of consciousness was of short duration. His wounds were dressed shortly afterwards at an Australian field ambulance. The following day he arrived at a general hospital where he was "held" for a week without any surgical treatment of his wounds. On July 25 he was transferred to another general hospital in the Canal Zone, and after 11 days there, reached a third general hospital in Palestine on August 4, 1942. He then complained of some headache on the left side, but his general condition was good. His wounds had healed except for one deep punctured wound in the left frontal region in the floor of which pus could be seen pulsating. On August 8, his skull was examined roentgenologically for the first time which demonstrated a comminuted fracture, with inward displacement of fragments of the inner table and a mottled appearance of the surrounding bone suggesting osteomyelitis. Numerous small metallic foreign bodies were seen some situated intracranially. There was also a small depressed fracture near the right parieto-occipital suture, but the wound in this region had healed.

On August 17, he was transferred to this Center. Two discharging sinuses were seen in the left frontal region and the depressed area of bone could be felt. The surrounding scalp was not edematous and its appearance did not indicate osteomyelitis. No abnormal neurologic signs were detected, although the patient complained of

BATTLE WOUNDS OF HEAD

occasional headaches and "giddy turns." Warm saline packs were applied to the discharging sinuses at frequent intervals until healing occurred, and on September 2, under local infiltration anesthesia, the depressed fragments of bone were elevated and removed. The surrounding bone was softened and vascular, from old osteomyelitis, but the dura mater was intact. The wound was left open and packed with vaselined gauze, and allowed to heal by granulation. This took about four weeks, and he was then transferred to a convalescent dépôt. He was reexamined on November 25, 1942. Except for complaints of occasional slight headaches and "dizzy turns," he was free of symptoms. A small superficial metallic foreign body was removed from the scalp, the depressed scar was excised and the scalp reconstituted over this area by a plastic operation. The depressed fracture in the right parieto-occipital area was not causing any trouble and was left alone. Primary healing occurred after these operations and the soldier returned to his training unit on December 11, 1942.

The pailous and prolonged convalescence of the next patient showed the importance of removing fragments of bone as well as metallic foreign bodies if serious complications are to be avoided.

Case 6—Pvt A P, age 21, received an "S W" just above the nasion on September 1, 1942. He was unconscious for about eight hours, and thereafter mentally dull. He was evacuated late the same day from the main dressing station, with a large foreign body retained, and a note "no time for excision of wound" made on his field medical card. He reached an Australian general hospital on September 3, where the wound was dressed. Next morning, a roentgenologic examination showed a large foreign body embedded in the frontal bone, with some splintered bone fragments indriven by it for about two centimeters. On September 5, the foreign body only was removed, under local anesthesia. Improvement in his mental condition followed and he was evacuated to this Center, where he only arrived on September 10.

By that time, he was complaining of headache and had marked photophobia. The wound was discharging pus freely and some debris could be expressed. Both fundi showed early papilledema, but there was no neck rigidity or pyrexia. Sulphapyridine was given in full dosage and, on September 17, the wound was reopened and the depressed fragments of bone were removed. The dura mater appeared to be intact and there was no sign of extra- or intradural suppuration. The wound was packed with sulphanilamide powder and vaselined gauze, and allowed to heal by granulation.

About October 7, the patient complained of frontal headache and had some evening pyrexia. A few days later, relief followed discharge of pus from the wound but advanced papilledema, with recent hemorrhage, was observed in both fundi. Spinal puncture yielded slightly turbid cerebrospinal fluid, at a pressure of 230 mm, containing 320 cells per cu mm, mainly lymphocytes. The protein content was 90 mg %. A further course of sulphapyridine was commenced and some remission of symptoms and pyrexia followed. By October 25, although the wound had healed, the papilledema had increased, and a subdural or brain abscess was suspected. Small volume encephalography was performed by spinal puncture, with oxygen, but unfortunately no gas could be made to enter the ventricular system. Patent subarachnoid pathways were seen, however, over both frontal lobes. The cerebrospinal fluid then had 220 cells per cu mm, mainly lymphocytes. The pressure was 140 mm and the protein content was 50 mg %. On November 20, the patient's condition had improved greatly, headaches were easier and the papilledema was subsiding. He was, thus, regarded as having had a condition similar to the so called "otitic or toxic hydrocephalus."

About three weeks later, a pulsating and inflamed swelling appeared at the site of the wound, and headaches, with pyrexia, recurred. Spinal puncture now yielded cerebrospinal fluid at a pressure of 450 mm, containing 110 cells per cu mm mainly

neutrophils. The protein content was 65 mg%. On December 12, operation was again performed under local anesthesia. The scar was excised and a thick pulsating dura exposed and opened by endothermy. A brain needle was inserted into the left cerebrum and, at a depth of two centimeters, entered an abscess cavity through a very thick capsule. About ten cubic centimeters of thick yellow pus were evacuated, the needle was withdrawn, and the wound closed, after spraying with sulphathiazole. On culture, a pure growth of *Staphylococcus aureus* was obtained, and administration of sulphathiazole in full dosage was started by mouth. The wound healed primarily, and, on December 20, spinal puncture yielded clear cerebrospinal fluid, at a pressure of 220 mm, with a cell count of 75 neutrophils per cu mm, and a protein content of 40 mg%. Further aspiration of the abscess did not reveal any pus.

Early in January, 1943, however, headache and papilledema reappeared. Encephalography was repeated, but again no gas entered the ventricles and the cortical pathways were patent. The cerebrospinal fluid now only had 35 lymphocytes per cu mm, although the pressure was still over 200 mm. On January 5, a brain needle with a silver cannula over it, was again inserted into the left cerebrum and through it, about 15 cc of pus spurted out of an abscess cavity at a depth of about two centimeters. This was followed by blood-stained fluid. The cannula was left *in situ* and the needle removed. Once again, a *Staphylococcus aureus* was grown from the pus. Only a little blood-stained fluid drained subsequently from the cannula, and it was removed on the third postoperative day.

Thereafter, the soldier's condition improved greatly and his symptoms completely disappeared, although the papilledema was loath to subside. A final attempt to locate more pus was made on January 16, but, although the abscess capsule was felt and penetrated, none could be aspirated. By January 20, the optic fundi had subsided considerably but were not yet normal. The pressure of the cerebrospinal fluid at spinal puncture was still nearly 300 mm, though the fluid was crystal clear. As this Center had to close down, the patient was transferred to another Neurosurgical Unit in the Middle East. News of his future progress will be awaited with interest.

Fortunately, all wounds of this group do not cause such vicissitudes, as can be seen from the next case, which also demonstrated how the brain could escape damage despite considerable damage to the skull.

Case 7—Pvt H T, age 26, received multiple "S W's" in the right side of his head on October 25, 1942, without any period of unconsciousness. He was wearing his steel helmet at the time. After the application of a dressing, he was hurried back to an Australian general hospital. On October 28, a roentgenologic examination of the skull showed a comminuted, depressed fracture in the right parietal bone and two small foreign bodies stuck in the skull more posteriorly. Little was done at the time beyond changes of dressing as no abnormal neurologic symptoms or signs were present, and there was a big rush of more serious casualties. He was evacuated some days later, and arrived at this Center on November 3, with his multiple wounds mildly infected and discharging. After shaving and thoroughly cleaning the scalp, and the frequent application of hot saline fomentations for two weeks, the wounds had healed. Operation was performed on November 17, when the edges of the scar were excised, the depressed fragments of bone removed, and the wound closed with drainage, after spraying with sulphanilamide powder. The foreign bodies were not causing any symptoms and were not removed. Healing took place rapidly, so that the patient was discharged to a convalescent depot on November 25, and returned to his unit on December 14, 1942.

Depressed fractures in the temporal fossa differ from depressed fractures of bones of the cranial vault, and may not need surgical interference, unless there is evidence of middle meningeal or subdural hemorrhage associated with them. Apparently, the temporal muscle affords this area some protection and increased blood supply, which helps the fragments to overcome any infection introduced at the time of wounding. The following case illustrates these points.

Case 8—Pvt H P age 37 was wounded on September 1, 1942, in the right temporal region by a large piece of shell which caused a long lacerated wound in the scalp and temporal muscle. The original notes were lost, but on arrival at an Australian general hospital on September 3, he was conscious, though drowsy and



FIG 5—Case 8. Anteroposterior view, showing a large depressed fragment of the right temporal bone, but no evidence of osteomyelitis.

slow in answering questions. At times, he was confused and incoherent. There was a slight weakness in the left side of his face, but otherwise no abnormal neurologic findings. The edges of the wound had been excised but not sutured. Roentgenologic examination of his skull was carried out and the report was as follows: "A stellate fracture in the right temporal bone, extending into the middle fossa and upwards into the parietal bone, no displacement of fragments visible." By September 7, his mental condition had improved and the facial weakness had lessened. On arrival at this Center three days later, the wound was discharging freely. As underlying osteomyelitis was suspected, a further roentgenologic examination was made, which showed that a large fragment of the right squamous temporal bone was depressed (Fig 5), but there was no sign of osteomyelitis. A few days later, a piece of latex rubber from the inside of his steel helmet came away, and thereafter healing proceeded

normally. No evidence of cerebral damage remained and spinal puncture yielded clear cerebrospinal fluid under normal pressure, so that further surgical interference was not considered necessary.

PENETRATING AND PERFORATING WOUNDS OF THE SKULL (GROUPS 4, 5 AND 6)

These wounds are by far the most difficult to deal with and present many problems, largely due to the entry of bacteria through the protecting barrier of the dura mater. Any form of hasty or incomplete operation will only do more harm than good, and they above all others, are best left alone until proper facilities for correct neurosurgical technic, controlled sulphamylamide therapy, and postoperative nursing are available, even if some delay results. The following methods of dealing with wounds of these groups were thus evolved.

Under anesthesia by local infiltration or pentothal sodium, a careful inspection of the wound or wounds, is made in the operating room, with the roentgenograms on a viewing box nearby. After a thorough skin preparation and excision of the edges of the wound, the extradural depressed fragments of bone are removed and the opening in the dura mater defined fully. To do this, it may be necessary to remove some undamaged bone. At the same time, hemorrhage from the dura is controlled.

Superficial debris, blood clot and destroyed brain are then gently washed away, by lavage and suction, from the track of the missile, usually with relief of intracranial tension and the return of pulsations in the area exposed. The number of indriven bone fragments has previously been counted and by careful exploration of the track of the missile and, with the help of the roentgenograms, they are then removed. It was surprising at times how deeply they had been driven in by even a small missile. The removal of all fragments is regarded as essential, and for this, a good headlight with adjustable focus, good suction, good retractors (or a Killam nasal speculum) and good assistance must be available. Frequently dirt, hair and other debris are found to have been taken in with them. On the other hand, it is considered only advisable to "go for" accessible metallic foreign bodies, as no abscesses or serious complications were encountered with retained metallic foreign bodies alone. With gentle technic very little bleeding need be caused by these procedures, and that can readily be controlled by endothermy or silver clips. The tracks are then filled with sulphathiazole or sulphadiazine cream, and in the absence of established infection, the opening in the dura mater is closed as securely as possible without causing undue tension. Only badly damaged and obviously necrotic portions of dura should be excised. Careful approximation of the edges of the tear in the dura mater is advocated wherever possible, to prevent hernia cerebri and leakage of cerebrospinal fluid. This precaution is particularly applicable, where the accessory nasal sinuses and mastoid air cells communicate with the wound in order to prevent the development of cerebrospinal rhinorrhea and intracranial aerocoele. An unusual case with these and other complications, following a self-inflicted wound which involved the left orbit, frontal sinus and frontal regions is

being reported elsewhere (Money and Stoller, 1943, in press) Collaboration with an otolrhinaryngologist in these cases is advised

Where the ventricular system has been penetrated or perforated by the foreign body, such closure is also desirable if an adequate toilet has been accomplished, but these wounds are so frequently fatal, that much experience in their treatment is hard to obtain. If cerebritis and/or brain abscess have already developed a soft rubber diam or narrow piece of corrugated rubber is inserted to the bottom of the track or abscess cavity and the dura closed around it. Then, after spraying with sulphathiazole or sulphanilamide powder, the scalp is closed around the diam. This diam is removed in 48-72 hours, if postoperative progress is satisfactory.

A prophylactic course of a sulphonamide by mouth is always commenced, or continued, if it has been started already. If meningitis and cerebritis were already established, then sulphadiazine was found to be the best drug, but it had to be given quickly and in large doses, up to 18 Gm by mouth or 12 Gm intravenously, in each 24 hours in order to maintain a concentration of over 10 mg % of the drug in the cerebrospinal fluid for the next 72 hours. These estimations, carried out by colorimetric methods, whenever cerebrospinal fluid is withdrawn at spinal puncture, are absolutely essential, for the correct regulation of the dosage of these drugs, as each patient absorbs and concentrates them at different rates and in different amounts. During the administration of such large doses of sulphonamide, it is necessary to give at least 3,000 cc of fluids daily by mouth, with sufficient alkali to keep the urine alkaline, in order to avoid hematuria and anuria, which occur if the drugs become precipitated as crystals in the otherwise concentrated and acid urine. Under this regimen these complications did not occur, although one fatal case of pontine hemorrhage was met with, but this appeared in an area of softening, about which, more will be said later. In unconscious patients, these drugs and fluids may have to be given with nasal feedings or intravenously. As a precaution against the production of blood dyscrasia and anemia, frequent blood counts and hemoglobin estimations should be made.

No experience was gained in the use of the electromagnet for the removal of metallic foreign bodies from the brain, as none was available, but as many of these foreign bodies are made of nonmagnetic metals, the use of this instrument is not considered worth while.

Postoperative dressings are done as infrequently as possible, provided the general condition of the patient is good and the wound is healing satisfactorily without much discharge. Adequate masking and the "no-touch technic" must be insisted upon, and it was found necessary to train nurses and orderlies especially in these methods. The appearance of a hernia cerebri or brain fungus calls for more frequent changes of dressing. Usually, the protruding brain is swabbed gently with a weak hypochlorite solution, sprayed with sulphathiazole powder and then covered with vaselined gauze. The intracranial pressure is reduced by spinal punctures, daily or as required.

Where there has been considerable loss or removal of bone from the

cranial vault, and where the wound has healed with a pulsating or depressed scar, adherent to the dura mater and brain cicatrix (especially in an area uncovered by thick hair), it is felt that bone grafting and plastic procedures are necessary, not only to relieve the usual complaints of local headaches, throbbing, giddiness on stooping, *etc*, which remain, but also from a cosmetic and psychologic point of view, for these soldiers always imagine that should they receive a blow of any sort on the "unprotected" area of brain, fatal consequences are likely. With this series, however, no case has so far been followed-up long enough to see whether bone grafting were necessary, and no further mention of it will be made here, except to say, that, of recent years and after similar injuries in civilian life, insertion of portions of cadaver skull, after 20 minutes boiling, has proved both simple and satisfactory. Several cases have already been operated upon successfully, in this fashion, in Middle East at another Neurosurgical Unit (verbal communication from Major P. B. Gscredit, R. A. M. C.).

The following case histories are presented to illustrate many of these points.

Case 9—Pvt. R. W., age 24, was blown off a motor cycle by the blast of a bomb, and sustained a wound in the middle of his forehead on September 12, 1942. After a short period of unconsciousness, he was confused and irritable when he reached a nearby South African field ambulance about two hours later. Operation was performed immediately, under general anesthesia. After toilet of the wound had been carried out, a comminuted depressed fracture, about the size of a shilling, was discovered, slightly to the left of the midfrontal line. On attempting to elevate the depressed area of bone, severe hemorrhage was encountered presumably from the sagittal sinus, and the wound had to be plugged with gauze. After insufflation of sulphanilamide powder and excision of the edges, the scalp wound was sutured over the gauze packing. The following day he was evacuated to an Australian general hospital, where, on September 14, the gauze packing was removed, without any further bleeding and the wound redressed.

He arrived at this Center on September 19. His wound appeared to be healing satisfactorily, but roentgenologic examination (the first) made shortly afterwards revealed several depressed fragments of bone, deeply indriven. As no abnormal neurologic signs were present, the wound was allowed to heal, and on October 13, under anesthesia with pentothal sodium, it was reopened and the indriven fragments of bone removed, without encountering any severe hemorrhage. Portion of the posterior wall of the left frontal sinus was involved and had to be removed, but the mucous membrane was intact. The deepest fragment had penetrated the dura mater to the side of the sagittal sinus. No signs of sepsis were found, so the wound was closed, and healed by first intention, with the aid of a short prophylactic course of sulphadiazine.

In this case, it appeared that the early surgical toilet and closure of the wound after excision, eliminated infection and complications, although the bone fragments could not be dealt with at the time.

The wound of the next patient also received prompt attention and healed primarily with the aid of sulphadiazine despite the retention of some indriven bone débris. Owing to its extremely inaccessible site, the question of removal of this metallic foreign body never arose. It was amazing what little serious damage it had caused considering the regions of the brain it had traversed.

Case 10—Pvt A W, age 27, received a severe penetrating "S W" of head, at about 1700 hours on September 19, 1942, when a shell exploded in the dugout he was occupying. He was not wearing his steel helmet at the time. Consciousness was lost at once but regained later at the regimental aid post, where a lacerated wound of the scalp was dressed. His left pupil was dilated and the plantar reflexes in both feet were "extensor" at the time. At midnight September 29, operation was performed at a casualty clearing station. A small wound near the bregma was explored, and a hole found in the skull over the superior longitudinal sinus. Some undriven spicules of bone were removed and there followed severe bleeding, which was controlled temporarily with gauze packing. After excision of its edges and a liberal insufflation of powdered sulphanilamide, the scalp wound was closed around two corrugated rubber drains. He was evacuated next day by air ambulance to a Neurosurgical Center in Egypt, where he arrived in a restless and semiconscious condition. There was paresis of the left arm and leg and the head and eyes were turned to the left. The left pupil was still larger than the right, and the left abdominal reflex was absent. Paresthesia and signs of meningitis were absent.

On September 2, the drains were removed and some serous discharge was observed. At 1800 hours, four Gm of sulphadiazine were given intravenously. Soon afterwards an attack of renal colic and hematuria occurred, so that no more of this drug could be given. The next day the sutures were removed. The edges of the wound appeared to be softening and bulging, and it looked as if an hernia cerebri were developing. Spinal puncture yielded blood-stained cerebrospinal fluid at a pressure of 180 mm, with a protein content of only 20 mg %, and containing 5.5 mg % of sulphadiazine. The wound looked better after withdrawal of sufficient fluid to bring the pressure down to 120 mm.

On September 25, the first roentgenologic examination of the skull was made, which showed "a small defect in the midline 2.5 cm posterior to the bregma, with some bone debris undriven for about 3 cm and a metallic foreign body with a diameter of 0.5 cm lying just to the right and behind the sella turcica." No further active treatment was undertaken, and by September 27, the wound had healed satisfactorily. The left pupil was still larger than the right but both reacted to light and accommodation. Diminution of sensation to pin-prick was noted in the areas of skin supplied by the 2nd and 3rd divisions of the right trigeminal nerve, and the left hemiplegia persisted, flaccid and hypotonic in the upper limb but more spastic in the lower limb where the tendon reflexes were exaggerated and the plantar response was "extensor."

Encephalography was performed on October 7, and the presence of any space-consuming lesion was excluded. Thereafter, the patient became more alert, and as voluntary power returned in his left lower limb he was able to walk with assistance as it was unlikely that he would become an efficient soldier again for at least a year, he was repatriated from Middle East early in December, 1942. The hemiplegia was still improving and no other symptoms were present.

Another patient had a single large retained metallic foreign body. It was not causing any symptoms, but the involvement of the sensorimotor area and its relative accessibility seemed to indicate the necessity for its removal, which was accomplished without incident and without finding any sepsis.

Case 11—Tpr T G, age 22, of the Royal Tank Regiment was wounded in the left parietal region on October 25, when his tank was attacked by a dive-bomber. A piece of bomb perforated his steel helmet, which he was wearing at the time. Loss of consciousness was only momentary. He remembered seeing a flash, and later, noticed that he could not control or stop moving his right hand. In it was a feeling

of "pins and needles," as if it were electrified, and when one of his mates touched his steel helmet at the site of the perforation he felt a "shock" in his right hand. This indicated that the sensorimotor area corresponding to the right hand had been damaged. His evacuation through a light field ambulance and an Australian casualty clearing station was rapid, with merely changes of dressing without roentgenologic examination or operation. On October 27, at a general hospital, a cock-up splint was applied to his right wrist on account of weakness in dorsiflexion. By November 7, when transferred to another general hospital in Palestine, the wound in his scalp had almost healed and except for slight clumsiness on skilled movements, the right hand had recovered its power, and sensations were normal. Roentgenologic examination was first made on November 19, which revealed "a punctured fracture in the left parietal bone, with a metallic foreign body in the underlying brain."

He was then sent to this Center, where removal of the foreign body and some depressed pieces of bone was carried out under local infiltration anesthesia. No evidence of infection was encountered and the wound healed by first intention. Lumbar puncture was performed early in January, 1943, when he returned from a convalescent dépôt for review. The intracranial pressure was normal and the cerebrospinal fluid quite clear. The right hand seemed normal in every way. His complaints of headaches, as the day wore on, were accounted for by an advanced grade of myopia, for which glasses had been ordered. He was considered to be fit for return to his unit, when they were supplied. There did not seem to be any indication for encephalography.

The next case had a somewhat similar injury, but a more parlous convalescence with probably some permanent disablement.

Case 12—Pvt H. P., age 26, of the Gordon Highlanders, was rendered unconscious by a mortar bomb at 0100 hours on the morning of October 24, 1942. He regained consciousness at 0440 hours, and applied his own field dressing to a wound of his scalp. He crawled back alone to safety and lay there till found at noon next day. He was evacuated rapidly down the line, arriving at a general hospital on October 26, where he complained of intense headache. A superficial scalp wound in the right frontal region was dressed after removal of some matted hair. On October 28, he was transferred to another general hospital in Palestine. On arrival there, on October 30, his headache was still severe. Neck rigidity was present and Kernig's sign was positive. Temperature 99.4° F, pulse 60. Roentgenologic examination of the skull revealed (Figs 6 and 7) a gap in the cranial vault through which a minute foreign body had traveled and lodged deep in the right frontal lobe. Several loose pieces of bone were present in the brain along the track of the foreign body.

Spinal puncture was performed and clear fluid was obtained, not under pressure, and removal of 5 cc relieved the headache. No record of any bacteriologic or cytologic examination was found. The wound was packed with sulphanilamide powder, and 2 Gm of sulphanilamide were given, by mouth, every four hours. The next day pyrexia was slightly higher, and, although the headache was less, the patient was drowsy. He was then transferred to this Center and on arrival, at 1800 hours, the wound was seen to be badly infected, with a foul purulent discharge, admixed with gas, from which hemolytic streptococci were grown on culture. Obvious signs of meningitis were present. Spinal puncture yielded yellow fluid, at a pressure of 200 mm, containing 520 neutrophils and 320 lymphocytes per cu mm. The protein content was 185 mg %. Three Gm sulphadiazine were given intravenously, and he was allowed a good rest after his journey.

On November 1, he was better, and the temperature had fallen to normal. Spinal puncture was repeated and yielded clear fluid, at a pressure of 150 mm, containing

BATTLE WOUNDS OF HEAD

200 neutrophils and 475 lymphocytes per cu mm. The protein content had fallen to 85 mg %. The sulphadiazine content of the cerebrospinal fluid was only 6 mg %, so a further three Gm were given intravenously and repeated 12 hours later.

On November 2 the signs of meningitis had disappeared but as the discharge from the wound was still copious and foul, operation was proceeded with, under anaesthesia with pentothal sodium. The edges of the wound in the scalp were excised



FIG. 6—Case 12. Anteroposterior view, showing the irregular gap in the right frontal bone, and the numerous irregular pieces of indriven bone. The small metallic foreign body is situated most inferiorly toward the midline.

and the hole in the bone enlarged, to define the tear in the dura mater. It was blocked by a piece of indriven bone, and when this was removed, pus and gas escaped from a brain abscess with relief of intracranial tension. The cavity of the abscess was explored and three more fragments of indriven bone and much necrotic debris were removed. The deepest fragment was 7 cm from the level of the dura and must have been very close to the lateral ventricle. The small metallic foreign body was not found. The cavity was irrigated, and a small soft tube inserted into its depths. The wound was sprayed with sulphanilamide powder and closed around the tube. A pure culture of hemolytic streptococci was grown from the pus of the abscess. As soon as the patient became conscious the administration of sulphadiazine was commenced by mouth, four Gm as an initial dose followed by two Gm every four hours.

The next day, his condition was satisfactory, and the sulphadiazine content of his cerebrospinal fluid had reached 12.5 mg %. Convalescence was thereafter uninterrupted,

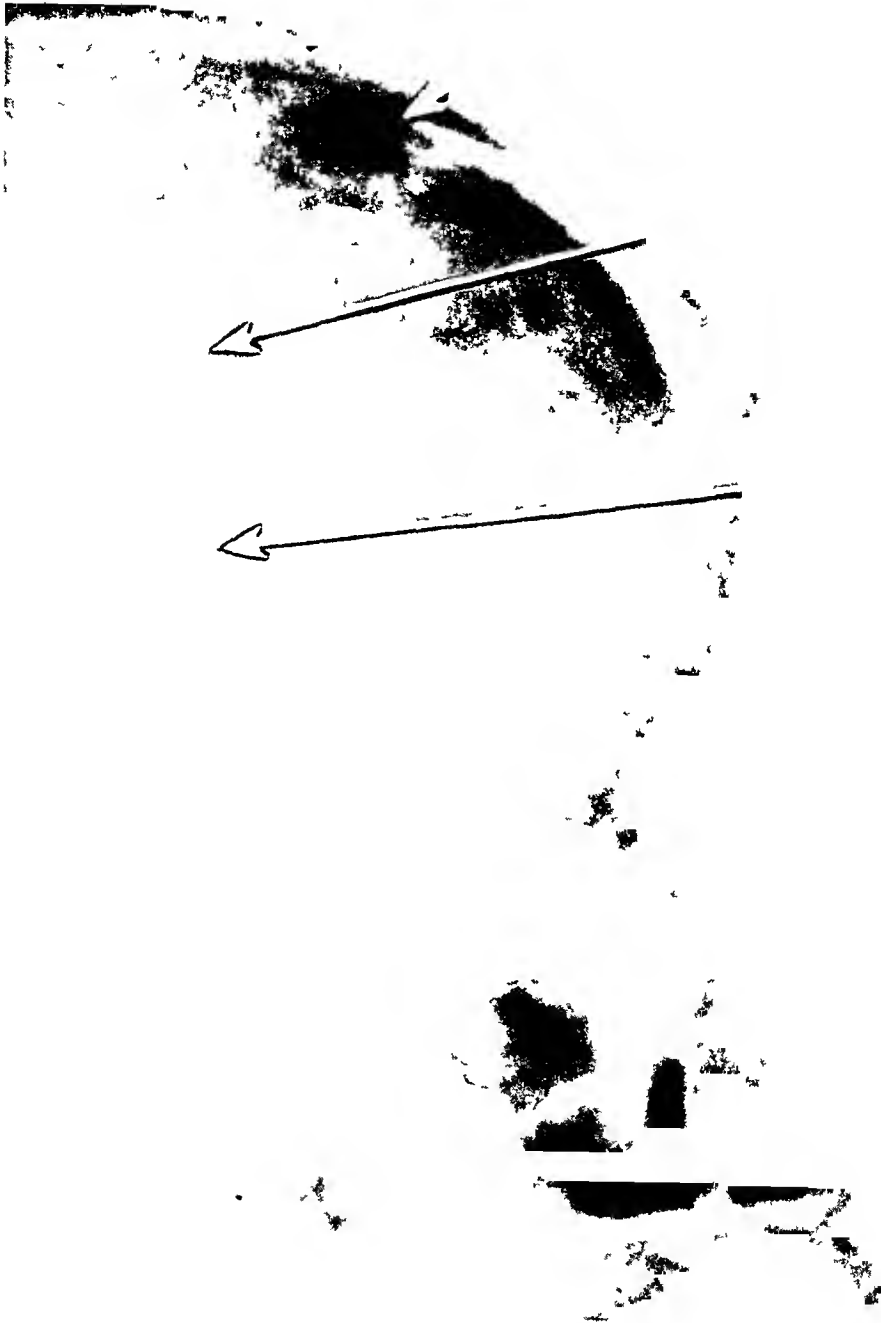


FIG 7—Case 12 Lateral view, again showing the irregular gap in the cranial vault and the undriven bone fragments along the track of the small missile, which is the most inferior and posterior foreign body

the tube was removed on November 8, and sulphadiazine was stopped after a total amount of 64 Gm had been given

By December 8, the abscess cavity had completely healed and he was sent to a convalescent depot. He returned for review early in January, 1943, feeling well except for headaches on exertion and giddiness on stooping down. The scar in the scalp at the side of the wound, was indrawn, somewhat tender, and pulsated during exertion. Encephalography was performed by the spinal route. The pressure of the cerebrospinal fluid was normal, it only contained two lymphocytes per cu mm,

and the protein content was 30 mg % Roentgenologic examination after the introduction of 30 cc of oxygen showed some generalized enlargement of both lateral ventricles in their anterior horns, with a definite "wandering" of the right anterior horn towards the cicatrix resulting from the abscess. The metallic foreign body previously seen had now separated into two parts, and both pieces were more superficial.

The patient was returned to the convalescent dépôt for further graduated training, but it was thought that bone grafting would be necessary later, and that he would probably not be fit to return to front line duties.

The fifth case selected from these groups was the only one of the series in which a fatality occurred, and demonstrated how serious infections of the wounded brain can still be, once they reach a ventricle, despite the advent of the sulphonamides. Unfortunately this case was one of the earliest in the series and was treated before a colorimeter was available and before the importance of determining the concentration of sulphadiazine in the cerebrospinal fluid of each patient (irrespective of dosage) was realized. Had this case been encountered later on, larger doses of sulphadiazine would have been given for a longer time in the first course, and operation for the removal of the remaining undriven bone fragments would have been undertaken much sooner. Full details, with the findings of the postmortem examination are submitted.

Case 13—W O (Class 2) E W H, aged 33, of the N Z E F, was admitted to a New Zealand field ambulance on July 8, 1942, with a history of having received a "S W" of head in the right occipital region 14 hours previously. Loss of consciousness was not recorded. The wound was cleaned with peroxide of hydrogen and dusted with sulphanilamide powder. He reached a general hospital next day where his wound was redressed. An entry on his field medical card stated "Not considered suitable for surgery. Skull does not appear to have been fractured. No roentgenograms taken."

On July 10, he was transferred to another general hospital in the Canal Zone, where a roentgenologic examination revealed a comminuted fracture in the right occipital region. Despite complaints of constant headaches, no surgical measures were instituted, as the wound was healing satisfactorily with daily dressings.

On July 24, he was evacuated by ambulance train to a general hospital in Palestine. Apart from headaches, his condition seemed good and the wound had almost healed. On July 30, his headache had become severe enough to warrant relief with morphia, and vomiting began. His temperature was elevated and total white cell count was 16,000 per cu mm. Roentgenologic examination showed "an area of bone necrosis in the right occipital region, ovoid in shape, and about 4×2.5 cm." Spinal puncture, performed next morning, yielded cloudy fluid, under pressure, containing 19,000 cells per cu mm. Hemolytic streptococci were grown from it, on culture. The administration of sulphapyridine in full dosage was commenced at once by mouth.

On August 1, his condition was critical, and his temperature had reached 105° F. Under anesthesia with pentothal sodium, the wound was explored and several depressed fragments of bone found. Some of them had punctured the dura mater, and on attempting to dislodge one of them severe bleeding began, probably from the lateral sinus. This fragment was removed and the bleeding was controlled by plugging with gauze. The exposed dura was then needled and some pus was aspirated at a depth of about two centimeters. Hemolytic streptococci were also grown from this pus. After dusting with sulphanilamide powder, the wound was packed with vaselined gauze and the administration of sulphapyridine continued by mouth.

During the next few days his condition improved somewhat and, on August 6 he was transferred to this Center. On admission, he complained of bilateral headache and nausea. There was marked rigidity of his neck. The abdominal reflexes were absent and a left-sided homonymous hemianopia was detected but no papilledema. Spinal puncture yielded turbid, yellowish fluid, at a pressure of 240 mm, containing 780 cells per cu mm. It was sterile on culture, but the protein content was high, *viz*, 250 mg %. The wound looked clean and was healing by granulation. A reexamination of the right occipital region, roentgenologically, showed (Fig 8) "an old comminuted fracture, extending across the lambdoid suture into the mastoid region. Some fragments of bone are still remaining, in the lower part of the opening and probably displaced inwards." In view of the failure of the sulphapyridine to clear up the meningitis sulphadiazine was substituted, two Gm by mouth every four hours.

On August 10, he was better clinically, although spinal puncture yielded fluid still slightly yellowish and turbid, at a pressure of 290 mm. The cell count had fallen to 265 cells per cu mm, but the protein content had risen to 400 mg %. (In the light of postmortem findings, it is believed that this indicated that ependymitis and pyocephalus were already present at that time.) As 40 Gm of sulphadiazine had been given, its administration was suspended.

On August 13, spinal puncture showed that, whereas the pressure of the cerebrospinal fluid was lower at 270 mm, the cell count had risen to 760 per cu mm. The protein content was 350 mg %. A second course of sulphadiazine was commenced by mouth, four Gm were given every six hours for four doses, followed by two Gm every four hours. Under local anesthesia, the wound was explored. Two pieces of loose bone were located deep to the dura and were surrounded by granulation tissue, but their removal caused profuse bleeding from the lateral sinus and further exploration could not be proceeded with.

Some improvement took place during the next few days and the sulphadiazine was again suspended, on August 17, after 38 Gm had been given. Three days later, however, intense headaches and vomiting returned. The patient became irrational, facile and slightly aphasic. Weakness and incoordination in the left upper and lower limbs were found, and the plantar reflex was "extensor." Bilateral grasping reflexes were present. Spinal puncture yielded slightly turbid yellow fluid, at a pressure of 440 mm, containing 580 cells per cu mm, and 700 mg % of protein. Roentgenologic examination was repeated, and two loose pieces of bone were still inside the cranium and deep to the posterior end of the wound. It was presumed that an abscess had formed in the right cerebral hemisphere, and was extending forward to involve the internal capsule and the lateral ventricle. Accordingly, under local anesthesia, the wound was again explored, and the two pieces of indurated bone were removed from the occipital lobe, at a depth of about three centimeters, followed by a small amount of blood-stained purulent discharge. A bur hole was then made 6 cm above theinion and 3 cm to the right of the midline, and the right cerebrum explored through it with a brain needle. The right lateral ventricle could not be located, and no abscess was found in the parietal or temporal lobes, but, in the direction of the wound, at a depth of 5 cm, a nonencapsulated abscess was located. There drained from the needle about 10 cc of pus, from which colonies of streptococci and staphylococci were grown. The patient's condition had improved slightly at the end of this procedure and on return to the ward, a third course of sulphadiazine was started with an initial dose of four Gm, followed by three Gm every six hours in nasal feedings.

By August 28, further improvement had occurred, especially in his mental condition. Headaches and neck rigidity were less, and he had been afebrile for 48 hours. Spinal puncture yielded clear fluid, at a pressure of 240 mm, containing only 85 cells per cu mm. The protein content had fallen to 190 mg %. The wound looked

clean, and there was no hernia cerebri. A brain needle was introduced into the right occipital lobe but only a little old blood was evacuated. It really looked as though the infection had been overcome at last, and next day, after 77 Gm had been given, the third course of sulphadiazine was stopped.



FIG 8—Case 13. Oblique view of right occipitomastoid region, showing the gap in the bone caused by the missile and the line of the fracture, with fragments of bone still present and probably indriven in the lower part of the opening.

This happy state of affairs was, however, shortlived and on August 31, a sudden relapse occurred. The patient became deeply unconscious, with dilatation of both pupils, and left-sided hemiplegia. Patellar and ankle clonus was elicited, and the plantar responses were "extensor" on both sides. A brain needle was passed through the bur hole and about 10 cc of serosanguineous pus were released from the occipital lobe, and

a further 10 cc of yellow pus at a depth of 7 cm from the temporal lobe, possibly from the lateral ventricle. After a temporary improvement, his condition rapidly deteriorated, and he died in a state of hyperthermia late that night.

A postmortem examination of the head was made next day by Major E. B. Jones, the pathologist to the Hospital. He found some infected brain tissue extruding from the wound in the right occipital region. The right lateral sinus had been opened by



FIG. 9.—Case 13. The midbrain has been cut through just where it joins the pons. The section on the right side is at a slightly higher level than on the left side. The undersurface of both cerebral hemispheres can be seen. Note the area of traumatic cerebritis in the right occipital lobe, and the softening and hemorrhage in the pons and midbrain.

the wound and its lumen had been obliterated by organized blood clot. An area of traumatic cerebritis was seen where the right occipital lobe was adherent to the edges of the tear in the dura mater at the site of the original wound (Fig. 9). The fore- and midbrain were removed by cutting through the upper part of the pons, and an extensive area of softening was revealed in the midbrain and pons, in which a recent hemorrhage had occurred (Figs. 9 and 10). The tentorium cerebelli and the rest of the brain were normal. Signs of chronic meningitis were present in the posterior fossa. The brain was then placed in formal-saline solution and, ten days later, horizontal sections were made, at intervals of 1.5 cm. through the cerebral hemispheres (Figs. 10

and 11) From the site of trauma in the posterolateral aspect of the right occipital lobe, and passing forwards and upwards till it reached the right lateral ventricle, was an area of softened brain tissue, in which hemorrhages had occurred and several abscesses had formed. The hemorrhages had apparently occurred at different times, some showing yellow discoloration. The right lateral ventricle was filled with material which looked like coagulated cerebrospinal fluid, mixed with organized pus indicating



FIG 10—Case 13. Horizontal section through the right cerebral hemisphere at a depth of 1.5 cm from the undersurface, photographed from below. Note the area of softened brain extending from the right occipital lobe to involve the lateral ventricle. It contains many small hemorrhages and abscesses.

localized pyocephalus of some duration. The right cerebral hemisphere was much larger than the left and had been dislocated across the middle line. This had interfered with the emptying of the left lateral ventricle, which was considerably enlarged and filled with clear fluid. The third and fourth ventricles were also filled with clear fluid, and thus, the pyocephalus in the right lateral ventricle must have shut off and was apparently proceeding to a stage of cure (such was the power of the sulphadiazine!) when the fatal pontine softening and hemorrhage occurred. No reason for this final complication can be offered, as neither the original wound or subsequent operative procedures involved

this region, and repeated blood examinations during the administration of the large doses of sulphonamides had not revealed any blood dyscrasia

The last case is presented to show that sepsis, and even an abscess may lie latent around a piece of indriven bone, without symptoms and without signs of increased intracranial pressure, another cogent reason for the removal of organic foreign bodies

Case 14—Pvt A H, age 31, received a severe "S W" of head with indriven bone fragments in the right parieto-occipital region, at 1000 hours, on July 24, 1942. He was wearing his steel helmet. He was only unconscious for a few minutes, and complained of blurred vision when he regained consciousness. Operation was performed at a casualty clearing station at 1800 hours, next day. The edges of the wound were excised, some pulped brain and superficial bone fragments removed, and the wound closed in two layers around a glove drain, after dusting with sulphamidamide. He was evacuated the same day to a general hospital where a course of sulphapyridine was commenced by mouth. Healing of the wound progressed satisfactorily but a roentgenologic examination, made on July 28, showed an annular area of bone missing from the right posterior parietal area, with a collection of indriven bone fragments deep to it.

It was realized that their removal was indicated, and he was transferred to a Neurosurgical Unit in Egypt on July 31. There were no abnormal signs detected on neurologic examination except a left homonymous hemianopia. During the next three weeks, the wound discharged some old blood clot and leaked a little cerebrospinal fluid on and off, but by August 22, it had healed except for a small button of granulation tissue. Routine encephalography was performed and showed a filling defect in the posterior horn of the right lateral ventricle. The cerebrospinal fluid, though clear, had five polymorphs per cu mm, and the protein content was 40 mg %.

It, thus, appeared to Maj P B Ascroft, R A M C, that the patient had a brain abscess, despite his satisfactory clinical condition, and on August 26, the wound was reopened, and the "track" in the brain was explored. Pus was encountered at a depth of 2.5 cm from a thick-walled abscess at this site, seven irregularly-shaped pieces of bone, up to two centimeters in length, were removed. Sulphathiazole cream was injected into the cavity, and the wound closed around a rubber drain. On culture of the pus, a staphylococcus was grown.

Convalescence was uneventful and, on September 7, he was transferred to this Center for down-grading, due to the persistence of the left homonymous hemianopia, before a final set of stereoscopic roentgenograms, taken on September 6, had been examined. These revealed seven or eight more pieces of indriven bone of various sizes, and the presence of another residual abscess had to be considered. Spinal punctures, on September 16 and 24 yielded clear cerebrospinal fluid, at normal pressure, only containing a few lymphocytes per cu mm, but the protein content of 50 mg %, on each occasion, indicated the persistence of a focus of infection. Accordingly on October 3, the wound was reopened, the scar in the dura mater defined, and the region of the old abscess explored. With great difficulty, five separate pieces of indriven bone were removed from depths varying between 3 and 5 cm, and around one of them a small amount of pus was found in an abscess cavity which was removed by suction. The wound was closed with drainage, after the insufflation of sulphanilamide powder. A pure culture of staphylococcus was again grown from the pus.

About three days later, symptoms and signs of meningitis appeared, despite a prophylactic course of sulphapyridine, but this infection gradually subsided with

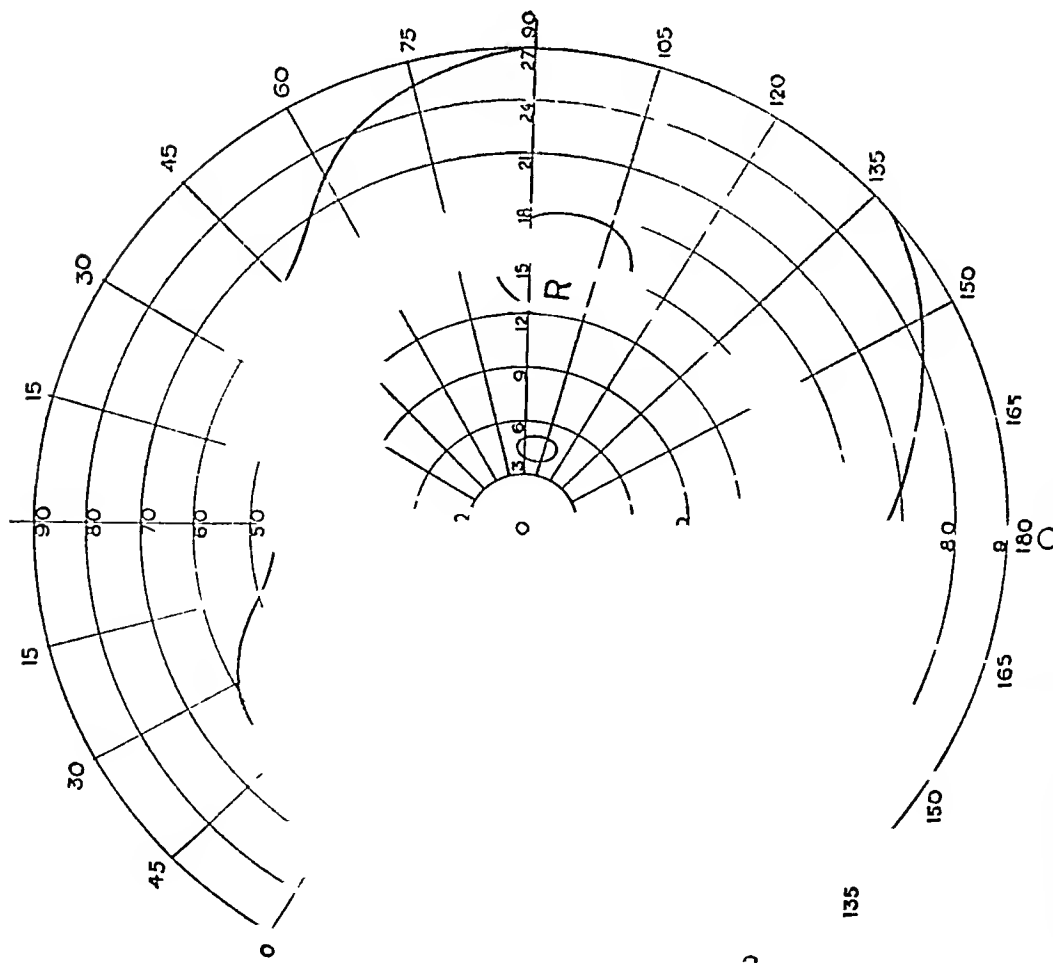
increased dosage of this drug, and a series of spinal punctures. On November 6 examination by Maj T Kingsley, the ophthalmologist to the Hospital, showed normal fundi but a complete left homonymous hemianopia (see Charts, Figs 12 a and b). Spinal puncture yielded clear fluid under normal pressure, with 15 lymphocytes per cu mm and a protein content of 45 mg %. Stereoscopic roentgenograms were again taken, and showed three indurated fragments of bone still *in situ*, but it was decided



FIG 11—Case 13. Horizontal section through both cerebral hemispheres, at a depth of 3 cm from the undersurface, photographed from below. Note the large size of the right cerebral hemisphere compared with the left, also the right lateral ventricle filled with congealed and organized cerebrospinal fluid and pus. The left lateral ventricle is enlarged but not infected.

to leave them there for the time being rather than risk stirring up another attack of meningitis, and he was sent to a convalescent depot for a month. His condition remained very satisfactory during that time, and he was repatriated after down-grading about the middle of December, 1942.

So far, little has been said about wounds of Groups 5 and 6, *i e*, perforating or "through-and-through" wounds, and penetrating wounds, where the missile has entered through the orbit and/or accessory nasal sinuses. Usually, there were greater degrees of neurologic disturbance and loss of



12 (a)—Case 14 Field of Vision Left Eye Complete homonymous hemianopia with macular sparing

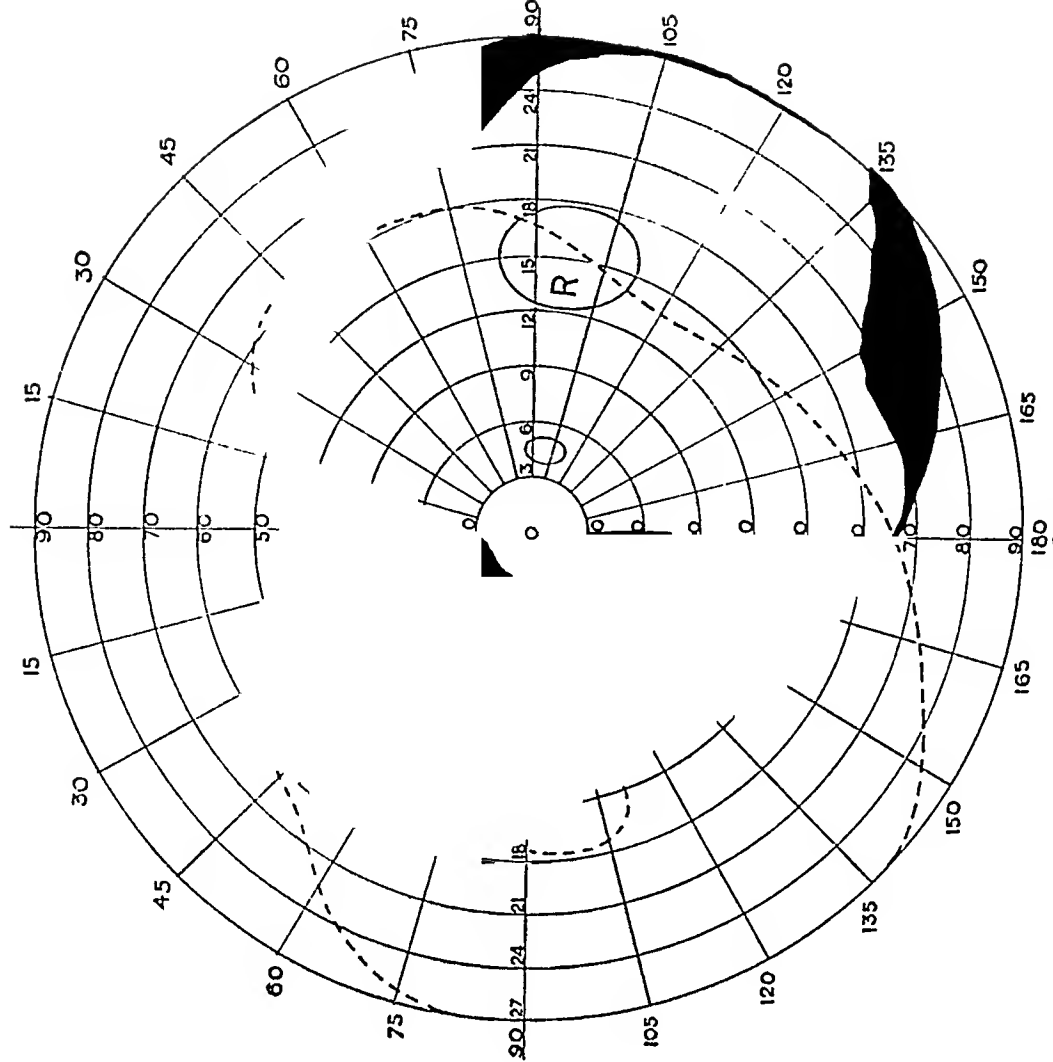


Fig 12 (b)—Case 14 Field of Vision Right Eye Complete homonymous hemianopia with macular sparing

function, both transient and permanent, associated with these groups of wounds, on account of the longer path taken by the missile, and the greater chances it had of causing cerebral damage, whether it passed in a transverse, sagittal or oblique plane. Many of them were fatal, or death took place in the forward areas before they could reach a Special Center. The prolonged period of initial unconsciousness and the added risk of the missile introducing virulent organisms from the accessory sinuses, or elsewhere, deeply into brain tissue or even the ventricular system, increased the hazards of their nursing and treatment, and made their prognosis worse. In general, the same methods of treatment, in the way of wound toilet, removal of indriven débris and bone fragments (especially from the orbital roof or frontal sinus), control of hemorrhage, and the use of sulphonamides are all applicable, but special attention should be directed towards gentle lavage of the track of the missile, followed by the injection of a sulphonamide cream, the provision of soft rubber drainage for a short period, and the prevention of reinfection, aerocele and fistula formation, from the involved sinus or orbit, by a careful repair or replacement of the torn dura mater as soon as practicable. A few cases of these groups were encountered in the present series, each with its own problems, but it is yet too early to assess their final results, and it is felt that consideration of them should be deferred.

DISCUSSION AND CONCLUSIONS

Most of the lessons to be learned from treating this series of cases have been discussed and pointed out as they occurred. They may be reiterated as follows:

- 1 The thoroughness of the initial examination and toilet of the wound is more important than the time factor at least up to four days, as long as prophylactic sulphonamide therapy is maintained during the period of waiting.

- 2 Surgeons, with field surgical units, must have a knowledge of neuro-surgical technic, and be provided with adequate facilities, if this class of wound is to be correctly dealt with in forward areas.

- 3 Under conditions existing in Middle East, it is better to stabilize these facilities at a place where the patients can be "held" after operation, and so arrangements should be made to transport the patient back as rapidly as possible, preferably by air ambulance, to a Special Center.

- 4 An alternative plan is the provision of a field surgical unit with operating theater and beds, entirely on wheels, which could keep pace with the advancing or retreating troops or be replaced by another similar unit when its accommodation was filled.

- 5 The removal of indriven bone fragments and inorganic débris is more important than the extraction of metallic foreign bodies.

- 6 Even minute missiles, making a small wound in the scalp and outer table of the skull, are likely to drive large comminuted pieces of the inner

table, deeply into the brain and cause more extensive damage than the size of the missile and the condition of the patient would indicate

7 Closure of the tear in the dura mater should be attempted in order to prevent the formation of hernia cerebri, cerebrospinal fluid fistula, and aerocele

8 Signs of unilateral local and focal damage to the brain do not call for extensive operations, in the absence of signs of compression, but they should be recorded from time to time by observers trained in neurology

9 The actual concentration of sulphonamide in the cerebrospinal fluid of every patient varies with the same dosage, and must be checked at frequent intervals by colorimetric methods to make sure an adequate concentration is being attained, and maintained, in case of intracranial infection

10 The advent of the sulphonamide group of drugs, especially sulphadiazine, has altered the outlook for wounds of the head entirely, and none should ever be despaired of, however badly infected and however serious the complications, nor can the final result be predicted

From a prophylactic point of view, it is felt that something further could be accomplished in the prevention of wounds of the head and subsequent infections by

(1) The provision of a more modern design of steel helmet, which would fit closer and lower down over the frontal, temporal, mastoid and occipital regions, and which would hinder the entry of rising foreign bodies from explosives which burst on the ground. The present design of steel helmet supplied to the British forces was designed, originally, to afford protection against bullets and the shrapnel of air-bursting explosives, now, not nearly so commonly encountered as splinters from bombs, high explosive shells and land mines. Major P. B. Ascroft, R.A.M.C. (verbal communication) has some very illustrative figures and charts, compiled from his series of some 700 cases, encountered during several Middle East campaigns, to prove these contentions. Their publication and his suggested design for a new helmet are awaited with interest.

(2) The issue of a general order that all troops should have the hair of the scalps closely clipped before going into battle. This would enable them to keep their scalps cleaner and greatly facilitate the work of the Medical Services in the recognition of wounds and their preparation for operation. It would also prevent long hairs and debris from being carried in by the missile. A somewhat analogous procedure exists in the Royal Navy, where personnel are advised either to discard all clothing when going into action, or put on brand new or clean clothes, to lessen the risk of sepsis from old dirty clothing being driven into their wounds.

(3) Every soldier should be given, to keep with his field dressing, a large standard dose of sulphapyridine or sulphadiazine, say four or six Gm., with instructions to take it himself, if able, or have it given to him by a stretcher

bearer, as soon as possible after being wounded. This would be an effective prophylactic for the next 12 hours.

SUMMARY

1 The surgical management of a series of battle casualties of the head, met with in the Middle East, is described and illustrated by numerous case reports.

2 Attention is drawn to certain anatomic and physiologic peculiarities of structures involved, as well as the effects of modern missiles used in Desert Warfare on these structures.

3 A classification of these wounds and the terminology applied to them in the British Army are submitted.

4 The necessity of providing adequate neurosurgical facilities, both in personnel and equipment, for dealing with these cases is pointed out and a general scheme outlined.

5 The lessons to be learned from the cases are discussed, and some prophylactic measures are suggested for future campaigns.

The thanks of the authors are gratefully extended to the undermentioned persons without whose assistance the treatment of this series of cases and the preparation of this paper would not have been possible.

1 The Director of Medical Services, G H Q Middle East, and the Consultant Neurologist, who authorized the establishment of the Unit as the No. 2 Head Center in the Middle East and made available certain special equipment and drugs.

2 The officers in charge of surgical divisions and surgical specialists of the other general hospitals who referred their cases for opinion and treatment.

3 The anesthetist, the ophthalmic and otorhinolaryngeal surgeons, the pathologist and the radiologists to the Hospital, and their staffs, who readily made their services available at all times.

4 Professor Howard Naffziger, M D, of the University of California Medical School and the British War Relief Society of Northern California, U S A, who donated special neurosurgical equipment to replace that previously lost by enemy action.

5 Pvt L R Withers, of the Hospital Staff, for the reproductions of the roentgenograms.

6 The Director General of Medical Services, Allied Land Forces, Australia, and the Deputy Director of Medical Services, Australian Imperial Force, Middle East, for permitting the publication of this article.

COMMUNICATIONS BETWEEN THE CORONARY ARTERIES PRODUCED BY THE APPLICATION OF INFLAMMATORY AGENTS TO THE SURFACE OF THE HEART*

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COMMUNICATIONS between the three major coronary arteries can be produced by surgical methods. It was shown experimentally by Stanton, Schildt and Beck¹ that trauma applied to the surface of the heart brought about the development of communications between one coronary artery and another. The type of trauma that was used in this demonstration was produced by abrasion of the surface of the heart. The epicardium was roughened and torn by means of special burs made for this purpose. We are now reporting upon the effect of various inflammatory agents applied to the surface of the heart. We are attempting to find a substance which, when applied to the heart, opens up or develops vascular channels between one coronary artery and another and at the same time does not produce harmful side-effects. A number of inflammatory agents have been used on the heart. Powdered beef bone was used by Beck,² aleuronat was used by O'Shaughnessy,³ talc was used by Thompson,⁴ and a mixture of aleuronat, starch, glycerin, commercial gelatin, water and lionite was used by Hembecker and Barton⁵. A study of this subject is obviously important. Our experiments may be regarded as an introductory study of this subject.

METHOD—Dogs were used. The material for study was introduced into the pericardial cavity either by making a small opening in the parietal pericardium or by an aspirating needle. The opening in the parietal pericardium was closed tightly by sutures. Three or more experiments were carried out with each substance that was selected for study. The pericardium was opened at the end of one, two and three weeks, under surgical conditions, and the reaction observed. Additional experiments were carried out with those substances that produced a favorable reaction.

Intercoronary communications were determined by a method worked out in our laboratory. We used a mixture consisting of barium sulfate 500 Gm, powdered gelatin 150 Gm and distilled water 850 cc⁶. This mixture was filtered while hot and was injected at a temperature of 45° C into the circumflex branch of the left coronary artery and into the right coronary artery. The heart was immersed in water at a temperature of 45° C during the injection. Injection of the arteries was done at a pressure of 200 mm mercury for three to five minutes. The specimen was chilled to solidify

* Aided by a grant from the John and Mary Markle Foundation

the injection mass. It was then fixed in a solution of formaldehyde. Roentgenograms were taken with the heart in such a position as to show the descending ramus of the left coronary artery. The degree of filling in the descending ramus of the left coronary artery was considered as an indication of communications between this artery and the two arteries that were injected. It would appear that the degree of filling has some quantitative significance. The injections were graded as absent, slight, intermediate, and good, and these terms are used throughout this paper as a measure of intercoronary arterial communications. Sections of the parietal pericardium and the epicardium were examined microscopically. When it appeared to be desirable, we attempted to measure the protective effect by ligating one of the arteries. This was done by ligation of the descending ramus of the left coronary artery at its origin several weeks after the substance under investigation had been applied to the heart. The mortality rate of these ligations and a study of the specimens gave information on this subject.

SUBSTANCES FOR STUDY—The most desirable substance appears to be one that produces a well vascularized type of granulation tissue without producing necrosis of the myocardium, severe exudation and cicatrization. Before beginning the study reported here, Beck had carried out experiments on various substances which he never fully reported. The substances investigated were powdered beef bone, surgical solution of chlorinated soda, kaolin, iron filings, tincture of iodine, ether, alcohol, saturated solution of sodium chloride, solution of glucose, horse serum, acids and alkalis. Of these, powdered beef bone produced the most favorable reaction and was used by Beck in human patients operated upon for coronary artery sclerosis. Chlorinated soda produced compression scars.⁷ Kaolin (hydrated aluminum silicate) was absorbed, leaving no reaction, and was found in mediastinal lymph nodes. Iron filings, tincture of iodine, ether, acids and alkalis produced hemorrhagic exudate and severe necrosis. The other substances produced little or no inflammatory reaction.

The only way to determine the effect of any substance is to try it. There was little information to aid us in the selection of materials for study. For this reason we are recording the effect of every substance we studied.

EXPERIMENTAL INVESTIGATIONS

Croton Oil—Croton oil was mixed with olive oil in the proportion of 1 to 10. Three cubic centimeters of this mixture produced death within five hours. Minute hemorrhages were present beneath the epicardium. There was no fluid in the pericardial cavity. Five cubic centimeters of a 4 per cent mixture produced death within 24 hours. Two cubic centimeters of a 1 per cent mixture produced death in 48 hours. A large quantity of bloody fluid was found within the pericardial cavity in each of these experiments. Capillary hemorrhages were present beneath the epicardium.

Croton oil was mixed with sesame oil in the proportion of 1 to 1000. Five cubic centimeters of this mixture was used in one experiment and one cubic centimeter was used in two experiments. These animals died in three days, two days, and seven days. One had acute cardiac compression produced by 200 cc of bloody fluid in the pericardial cavity. The thoracic and abdominal cavities contained straw-colored fluid.

The liver showed focal necrosis. The mediastinal tissues in these experiments showed hyperemia. Fibrin was deposited upon the epicardium within a few days. Microscopically, a deposition of fibrin was found on the epicardium and parietal pericardium and these structures showed acute inflammation.

Croton oil, even in high dilution, is a strong irritant and should not be used for this purpose.

Santal Oil—Santal oil was used in three experiments. Three cubic centimeters produced death within five days in each experiment. A large quantity of turbid fluid was found in the pericardial cavity. A severe inflammatory reaction was present beneath the epicardium and also in the parietal pericardium. Microscopically, there was evidence of acute inflammation in the epicardium with necrosis of the adjacent myocardium. There was an infiltration of polymorphonuclear leukocytes and large round cells in these structures.

Santal oil is a strong irritant when injected into the pericardial cavity and should not be used for this purpose.

Formaldehyde—Formaldehyde was used in six experiments. Two cubic centimeters of 10 per cent solution was used. In three experiments death occurred within seven days. Fluid was found in the pleural and pericardial cavities. In one experiment death occurred two months later from chronic cardiac compression. The parietal pericardium and epicardium were sealed together and compression developed from the contracture of this scar. In two experiments the descending ramus of the left coronary artery was ligated at its origin ten days after the introduction of the formaldehyde. Death occurred almost immediately after ligation of this artery in each experiment. The coronary arteries were injected and in one of these specimens there were some intercoronary communications present and in the other specimen there was no evidence of intercoronary communications.

Formaldehyde is a strong irritant. It produces exudate and compression scars. It may exert some slight effect upon the production of intercoronary communications but the reaction is too severe for our purpose.

Neutral Acriflavine—Neutral acriflavine was used in a 30 per cent solution. Two cubic centimeters were introduced into the pericardial cavity in three experiments. One animal died four days later, one died six days later, and one was killed seven days later. Serosanguineous fluid was found in the pericardial and pleural cavities in each of these animals. The parietal pericardium was thickened and a few fibrinous adhesions to the heart were present. Subepicardial inflammation and degeneration of adjacent myocardium were found. Many small blood vessels were present in the pericardium.

Acriflavine is a strong irritant and should not be used for our purpose.

Typhoid Vaccine—Typhoid vaccine (one billion organisms per cubic centimeter) in doses of two cubic centimeters was introduced into the pericardial cavity in three experiments. These animals were killed at the end of one, two and three weeks. The epicardium and parietal pericardium appeared to be normal in each experiment.

Typhoid vaccine produced no recognizable reaction in these experiments. We should like to suggest that biologic reactions, such as the Schwartzman reaction, should be investigated in reference to this problem.

Sodium Morrhuate—Sodium morrhuate (Parke, Davis, 5 per cent) was injected into the pericardial cavity in three animals in doses of three cubic centimeters. At the end of one week the parietal pericardium showed a severe hemorrhagic inflammatory reaction consisting of red corpuscles, fibrin, edema and polymorphonuclear leukocytes. There was also an increase in the size and number of blood vessels. Fibrinous adhesions to the epicardium were everywhere present. These did not bleed when broken during operation. The epicardium was thickened and showed a similar reaction. There was little or no fluid between pericardium and heart. At the end of 19 days the inflammatory reaction had almost entirely disappeared. There were no adhesions and epicardium and parietal pericardium appeared to be normal. Microscopically, the parietal pericardium showed resolution of the inflammation with some residual fibrosis. There was no increase in vascularity. At the end of four months the epicardium and parietal pericardium appeared grossly normal and, microscopically, showed some slight fibrosis.

The right coronary artery and the circumflex ramus of the left coronary artery were injected with barium sulfate-gelatin mixture in two specimens that had received sodium morrhuate four months previously. In each of these, the descending ramus of the left coronary artery showed slight injection. The amount of barium present was within the limits found in normal hearts injected in the same way.

Sodium morrhuate produces an inflammatory reaction together with an increase in vascularity during the early stages. These changes are of a temporary nature and disappear after a few weeks. For our purpose it is desirable to select a substance that exerts an effect on vascularity for a long period of time.

Sodium Ricinoleate—Sodium ricinoleate ("Soricin" Merrill Co., 5 per cent) was injected in quantities of three cubic centimeters in each of three animals. At the end of one week the epicardium and parietal pericardium showed severe inflammatory reaction. Microscopically, a marked extravasation of red blood cells was found beneath the epicardium and also in the parietal pericardium. In one animal that was operated upon for purposes of examination, ten cubic centimeters of serosanguineous fluid was found in the pericardial cavity. Death occurred five days later, and large quantities of serosanguineous fluid were found in the pleural and pericardial cavities. The heart was examined for intercoronary communications and no barium went across to the noncannulated artery. In another experiment the heart was examined at the end of 12 days. At that time, there was no exudate on the heart or on the parietal pericardium. The inflammatory reaction seemed to have subsided markedly. In another experiment the parietal pericardium was opened at the end of 24 days. The inflammatory reaction had almost completely subsided. The parietal pericardium was slightly thickened. There were no adhesions and there was no fluid in the pericardial cavity. The animal was killed at the end of four months. The heart and pericardium appeared normal. The coronary arteries were injected and good intercoronary communications were demonstrated.

Sodium ricinoleate produces a reaction similar to that of sodium morrhuate. A severe inflammatory reaction is produced early. Later the inflammation subsides. There is an early increase in vascularity but it seems to subside as the inflammation subsides.

Iodized and Chlorinated Oil—Iodized and chlorinated oil ("Iodochoral," Searle) was injected in three experiments in quantities of four cubic centimeters. One animal died at the end of seven days. Large quantities of fluid were found in the pleural and pericardial cavities. A severe cellular reaction was present in the pericardium. There

was no evidence of intercoronary communications in the injected specimen. In another experiment the pericardium was opened at the end of 19 days. A few fine adhesions were found. The inflammatory reaction was mild and almost absent. The oil was saponified and appeared as plaques in the epicardium. At the end of three months the reaction had subsided and little or no fibrosis of the pericardium was present. The coronary arteries were injected in this and also in the third specimen at the end of three months and good intercoronary communications were present in each specimen.

This substance produces an early, marked inflammatory reaction which has a tendency to subside after a few weeks. It seems to favor the development of intercoronary communications but the effect is too severe to be used in patients.

Tragacanth—Tragacanth in doses of two Gm was used in three experiments. Cardiac compression developed in two experiments. One animal died in two days, the other died in 15 days. The latter was explored by operation the day before death. At operation, fluid was found in the pericardial and pleural cavities. The fluid was removed. The parietal pericardium was thickened and densely adherent to the heart. The adhesions did not bleed when broken. Fluid rapidly reformed in the pericardial and pleural cavities and produced death the following day. The third animal continued to live and was killed at the end of three months. The parietal pericardium was thickened and was adherent to the heart. The inflammatory reaction had subsided. Fibrosis and some blood vessels were found in the pericardium. The three hearts were injected with barium. The animal that died in two days did not show any of the barium in the descending ramus of the left coronary artery. The other two specimens showed a moderate amount of the barium in this artery.

Tragacanth produces a severe exudative reaction and should not be used.

Talc—Magnesium silicate, Gm 3, was introduced into the pericardial cavity in three experiments. An inflammatory reaction developed in a few days in the parietal pericardium and epicardium of these animals. These tissues had a gelatinous exudate and were joined by fibrinous adhesions which were easily broken and from which there was no bleeding. Later, the talc collected in localized areas which became walled-off. Elsewhere the reaction was mild and the epicardium and parietal pericardium resembled the normal. At the end of three months thick avascular scar tissue was found in the pericardium. In one experiment scar tissue produced signs of cardiac compression. In a series of ten additional experiments, three Gm of talc was introduced into the pericardial cavity and the animals were allowed to recover. Two weeks after the talc was introduced, these animals were reoperated upon and the descending ramus of the left coronary artery was ligated at its origin. Three of the animals recovered from this ligation and seven died.

On the basis of these experiments, it appears that talc did not exercise a beneficial effect when this artery was ligated. These results were similar to those obtained following ligation of the descending ramus of the left coronary artery in control experiments. They do not agree with the beneficial results reported by Thompson⁴.

Silicon—Two Gm of powdered silicon (Merck) was introduced into the pericardial cavity of three animals. The early reaction consisted of inflammation and adhesions. Later on, these adhesions did not seem to be well vascularized, and there was no bleeding when the adhesions were broken. There was some thickening of the peri-

cardium All of the animals lived and were killed at the end of three months In two animals the coronary arteries were injected with barium as usual There was no evidence of intercoronary communications in these specimens

The reaction produced by silicon is not favorable

Sand—Sand (Merck), ten Gm was used in each of three experiments At the end of seven days adhesions were present between the parietal pericardium and epicardium These were easily broken without bleeding The surface of the heart was reddened and injected At the end of 21 days the inflammatory reaction was mild The sand had collected posteriorly at the base of the heart At the end of three months' time a few adhesions were present The inflammatory reaction had subsided The parietal pericardium was thickened The coronary arteries of two specimens were injected in the usual way at the end of three months One specimen showed good filling of the descending ramus of the left coronary artery and the other specimen did not show any barium in this artery

The reaction produced by sand is not favorable

Water Glass—Water glass, which is a solution of sodium silicate, was placed in the pericardial cavity in five animals The amount used varied from one to five cubic centimeters Death occurred in each experiment within two weeks The tissues that came into contact with the water glass appeared brown, as though they had been burned There was much exudate in the pleural and pericardial cavities

Water glass is a strong agent causing exudation and necrosis

Agar—Agar in powdered form, in doses of three Gm, was used in four experiments Death occurred in each experiment 1, 3, 10 and 11 days later from cardiac compression The pericardial cavity was filled with thick serosanguineous fluid Slight hyperemia of the parietal pericardium and epicardium was found Some fibrinous adhesions were present The reaction in the pericardium and epicardium varied from a mild to a moderately severe inflammation Fluid was found in the pleural cavities and also in the abdomen The right coronary artery and the circumflex ramus of the left coronary artery were injected Moderate injection of the descending ramus of the left coronary artery was found in one specimen and no injection was found in the other three specimens

The effect of agar is not favorable

Cotton—Cotton gauze was used in four experiments One layer of surgical gauze was placed between heart and pericardium An inflammatory reaction was found early, with adhesions which were well vascularized Later, these adhesions became dense and the inflammation subsided The vascularity was less at the end of three months but blood vessels were found in the adjacent scar There was no formation of fluid in the pericardial cavity The coronary arteries were injected in three specimens at the end of three to four weeks, and one specimen showed a slight amount of barium present in the descending ramus of the left coronary artery, and two specimens showed no injection of barium in this artery

A paste consisting of 0.4 Gm of finely cut cotton and two Gm of starch was introduced into the pericardial cavity in five animals Subsequent examination showed adhesions between the parietal pericardium and the heart The adhesions were dense in those locations where cotton had collected between heart and pericardium Elsewhere the adhesions were easily broken The parietal pericardium showed slightly increased vascularity The descending ramus of the left coronary artery was ligated and one animal survived and two died The coronary arteries were injected with barium and

the intercoronary communications were good in two specimens, slight in one specimen and absent in two specimens

Cotton produces a relatively mild inflammatory reaction early with the formation of blood vessels but later the vascularity becomes less marked. Cotton is not particularly effective in increasing the vascularity in these structures.

Aleuronat—Aleuronat was introduced into the pericardial cavity in four experiments. Three Gm was used in each. One of these was examined at the end of eight days. The parietal pericardium bled freely when it was incised. It was greatly thickened and showed fibroblasts and cellular infiltration. A large quantity of bloody fluid was present in the pericardial cavity. It clotted upon standing. There was a deposit of fibrin upon the epicardium and many adhesions were present. This animal died at the end of 17 days from acute cardiac compression due to fluid in the pericardial cavity. The pleural cavity also contained fluid. The other three animals developed compression of the heart and died in 10, 24 and 30 days respectively. In each of these, thick sero-sanguineous fluid was present in the pericardial and pleural cavities and clear straw-colored fluid in the abdomen. The parietal pericardium and epicardium were thickened and were avascular. There was a marked deposition of fibrin on the heart and there were many avascular adhesions to the heart. The coronary arteries were injected with barium in these specimens and in none of them was there any evidence of intercoronary communications.

Aleuronat produces a severe, exudative, inflammatory reaction. There was an early increase in vascularity in the parietal pericardium of one animal but in three hearts in which the coronary arteries were injected intercoronary communications were not found.

Lionite, Aleuronat and Starch—(Hembecker and Barton)⁵ A mixture of lionite, aleuronat and starch was made in the proportions used by Hembecker and Barton. Eight to ten Gm of this mixture was placed in the pericardial cavity in ten animals. One cubic centimeter of sodium morrhuate was applied to the surface of the heart before this mixture was introduced. These animals survived this procedure, and two months later the descending ramus of the left coronary artery was ligated at its origin. Four of these survived and six died. This mortality rate is similar to that obtained in control experiments. The deaths occurred within 24 hours after ligation. Early death after ligation of this artery occurred in normal hearts and in those specimens in which the preparation had provided little protection to the heart. The arteries in these six specimens were injected with barium and they showed intercoronary communications to be of intermediate grade in two, slight in two, and absent in two. The four animals in which recovery took place after the artery was ligated were killed several months later. Good intercoronary intercommunications were found in each specimen. Arterial ligation is an effective stimulus in producing these communications. The infarct in these specimens was large in three and intermediate in size in one. It is to be noted that the size of the infarcts also indicated that the protection afforded to the heart was not great. In other words, the blood-bath to the ischemic myocardium was not sufficient to prevent the usual necrosis and replacement of scar tissue. Cardiac compression developed in one of these experiments after the artery was ligated. The compression scar was removed and the condition was cured.

Nine additional experiments were undertaken using the Hembecker-Barton mixture. One cubic centimeter of sodium morrhuate was applied to the surface of the heart and eight to ten grams of the lionite-aleuronat-starch mixture was introduced. Four of these

animals died of cardiac compression in 11 days to six weeks after this material was placed in the pericardial cavity. One died of distemper two weeks later. Four animals remained alive in this series and three of them developed cardiac compression. The compression scars were removed by operation, and all three recovered. These animals were killed several weeks later. The specimens of the entire group were studied for intercoronary communications. Three specimens showed no evidence of intercoronary communications, two showed slight filling of the descending ramus of the left coronary artery and four showed intermediate filling of the artery. Good communications were not found in any of these specimens.

Microscopic study could not be made because of the lime. A severe inflammatory reaction with exudation was produced by these inflammatory agents. There was a great tendency for cardiac compression to develop following the use of these substances. The lime had a tendency to collect in masses posteriorly to the heart.

These substances, according to our studies, are not effective in producing intercoronary communications, and the reaction is severe. Our results are not as favorable as were those obtained by Hembecker and Barton.

Human Skin—Three Gm of dried, sterilized human skin, cut into small pieces, was placed in the pericardial cavity in three experiments. Death occurred in 2, 9 and 10 days. The pericardial cavity contained large quantities of exudate which had the appearance of pus. The epicardium was covered with a deposit of fibrin. The parietal pericardium was several times its normal thickness and, in one specimen, there were numerous blood vessels. The inflammation in the pericardium was severe. The coronary arteries were injected with barium. One specimen showed good filling of the descending ramus of the left coronary artery, one showed slight filling and one showed no filling of this artery.

Skin had a severe exudative reaction and is not satisfactory.

Hembecker-Barton Mixture, Sodium Morrhuate and Human Skin—Eleven experiments were made in which eight Gm of Hembecker-Barton mixture, 1 cc sodium morrhuate, and one Gm human skin were introduced into the pericardial cavity. Death occurred in two of these animals from compression, death occurred in three from distemper, six were killed after four months. The coronary arteries were injected with barium in the specimens' and the communications were graded as absent in four, intermediate in three, and good in three. It appeared that there was an increase in intercoronary channels in these experiments.

We believe it is advisable to determine what single substance produces the most favorable reaction and not to use many different substances at one time.

Asbestos (calcium and magnesium silicate)—Three Gm of calcium and magnesium silicate, in the form of asbestos, was placed in the pericardial cavity in three experiments. At the end of one week the parietal pericardium was slightly thicker than normal and was well vascularized. Brisk bleeding occurred when it was cut. It was adherent to the heart and the adhesions bled when they were broken. A few cubic centimeters of fluid was present in the pericardial space. The surface of the heart appeared to be hyperemic. Marked cellular infiltration was present at the end of one week. The cellular reaction subsided later, and many arterioles and capillaries were formed at the end of two weeks (Figs 1 and 2). The epicardium lost its identity and the inflammatory process was in direct continuity with muscle fibers. The mediastinal tissues and fat showed increased vascularity. These tissues bled when cut. When the lung became adherent to the outer surface of the parietal pericardium the surfaces bled.

freely when separated. At the end of four months the sections showed an increased number of blood vessels and also some scar tissue. The cellular reaction had generally subsided at that time, and foreign body giant cells were present. The coronary arteries were injected with barium at the end of three to four months. The filling of the descending ramus of the left coronary artery was good in two specimens and was slight in one specimen.

Many additional experiments were carried out with this form of silicate (asbestos). It was found that the amount of asbestos that produced the most favorable reaction was about 0.1 or 0.2 Gm. Large amounts occasionally produced a subepicardial hematoma. In one experiment a walled-off collection of fluid between parietal pericardium and heart produced compression of the heart. Thick dense epicardial scars were pro-



FIG. 1.—Photomicrograph of visceral and parietal pericardium showing foreign body reaction produced by silicate. Blood vessels are shown (X94)

duced by large quantities of asbestos. In several experiments fluid was found in the pleural cavities. When the coronary arteries were injected with barium intercoronary communications were present in every specimen.

Nine experiments were carried out in which about 0.5 Gm of silicate in the form of asbestos was used. These experiments were allowed to proceed for a period of two weeks. At the end of this period operation was carried out and the descending ramus of the left coronary artery was ligated at its origin. Six of these animals survived ligation of this artery, three died. The coronary arteries of these three specimens were injected with barium and good intercoronary communications were found in two of the specimens. The six animals that survived the operation were killed several months later and the size of the infarcts noted. In one of these specimens there was no infarct, in three specimens the infarct was small, and in the remaining two specimens the infarct was classified as intermediate in size. There were no large infarcts.

In our experience, the mortality following ligation of the descending ramus of the left coronary artery at its origin in normal animals was 35 out of 50 experiments, or 70 per cent. In these nine experiments treated with asbestos, six animals survived a second operation at which this artery was ligated, a mortality of 33 per cent. We interpret this as a reduction in mortality. We can also state that the infarct was of

smaller size in the experiments in which asbestos had been used. For a discussion of mortality and size of infarct in 50 normal hearts in which the descending ramus of the left coronary artery was ligated at its origin, the reader is referred to the article by Stanton, Schildt and Beck¹

Another series of ten experiments was carried out in which the surface of the heart was rubbed by a bur in such a way that the epicardium was torn and some of it was removed in shreds. In these experiments 50 to 100 milligrams of asbestos was rubbed into the surface of the heart by a bur. These animals survived this procedure. Most of them showed an elevation in temperature of about one degree centigrade for a week or ten days. A compression scar did not develop in any animal. One week later the

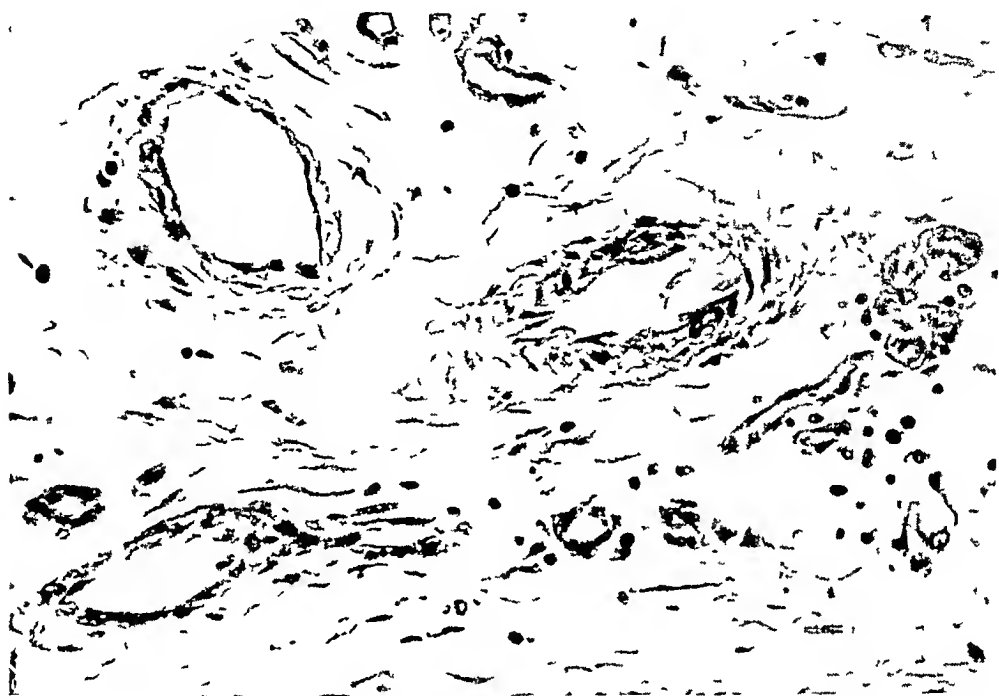


FIG 2—Photomicrograph showing arteries and veins produced by silicate on surface of heart (X297)

animals were operated upon again and the descending ramus of the left coronary artery was ligated at its origin. Seven of these animals survived ligation and three died, a mortality of 30 per cent. One of these died a few minutes after the artery was ligated and the injection specimen showed good intercoronary communications. Two died within 24 hours after ligation of the artery. The seven animals that survived ligation of the artery were killed at the end of six weeks. Two of these showed focal areas of myocardial fibrosis and no gross infarct, two had infarcts of intermediate size, and three had large infarcts. Each of these specimens showed good intercoronary communications. The common arterial bed in these specimens was produced by the inflammatory reaction produced by abrasion and by the asbestos plus the delayed stimulus of the arterial ligation itself.

A paste consisting of 0.2 Gm of asbestos and a small amount of tragacanth was placed in the pericardial cavity in six animals. One of these died one month later and examination showed fluid in the pleural cavities. Ligation of the descending ramus of the left coronary artery was carried out in four experiments. Two of these animals recovered and two died. Injection of the arteries with barium in these four hearts showed good intercoronary communications in the two specimens where recovery occurred, slight filling in another and no filling in another.

The effect of a paste made of tragacanth and asbestos was not as good as that with the powdered asbestos alone.

DISCUSSION —On the basis of these experiments it appears that silicate in the form of powdered asbestos produced the most favorable reaction. The inflammatory process brought about by asbestos was well vascularized. Amounts of about 0.2 Gm. distributed over the entire surface of the heart produced a more favorable reaction than did a larger quantity. It is slightly exudative in its effect but this is not severe and it does not preclude its use when employed in small quantities. It does not produce compression of the heart due to the formation of scar tissue. The inflammatory effect persists over a period of several months. We have used it on human patients and the effect was satisfactory. The wound in the chest wall healed nicely in these cases. Measurements of the beneficial effect are indicated by data obtained by ligation of the descending ramus of the left coronary artery at its origin. Mortality in 50 normal animals following ligation of this artery was 68 per cent. Mortality in animals in which asbestos had been applied to the surface of the heart previous to ligation was 32 per cent (six out of 19 animals). The size of the infarcts in the latter group was smaller than in the control group. Indeed, in a few of the specimens treated by asbestos there was no infarct after the descending ramus of the left coronary artery was ligated. In the control group a definite infarct always developed after ligation of the artery. Also intercoronary communications were better developed in the specimens in which asbestos had been used as compared with the intercoronary channels found in normal hearts.

Some of the substances used in the experiments produced death. This was brought about by exudation of fluid or by the development of compression scars. Some of the substances produced little or no reactions, others produced a rather indifferent degree of vascularization, others produced good vascularization early but after several weeks the degree of vascularization became less marked. It seems to be desirable to use one substance rather than a combination of substances. It needs scarcely be stated that one should not be indiscriminate in what substance is placed in the pericardial cavity and also in the amount used.

Hembecker and Barton carried out experiments in which a mixture of gelatin, albumen, starch, glycerin, water and lionite was introduced into the pericardial cavity. In some experiments these authors also used sodium morrhuate. After these substances were introduced the pericardium was closed and then the pericardium was sutured to the restiosternal tissues. Fourteen animals were prepared in this manner. Four to 12 weeks later, these animals were again operated upon and the descending ramus and the circumflex ramus of the left coronary artery were ligated about one centimeter from the aorta. Eight of the 14 animals died and six survived. Infarcts were not found in these specimens.

We carried out experiments in which we tried to repeat this procedure. We were not able to get any animals to survive ligation of both of these arteries in one step. According to our studies the reaction produced by these irritants was not as satisfactory as that produced by powdered asbestos. This mixture of substances produced death in some of our experiments by the

formation of fluid. The tissues, as found in our experiments, were not as richly vascularized as we found after the use of asbestos.

O'Shaughnessy reported favorable results by the use of aleuronat. We found that aleuronat produced a severe exudative reaction, with an early increase in vascularity but later, no increase in vascularity was found.

Thompson reported favorably on the use of talc. Our experiments failed to confirm his highly beneficial results. It is interesting to note the different reactions produced by various silicates. Talc is a soft, unctuous mineral consisting of magnesium silicate. Asbestos is fibrous magnesium and calcium silicate. Water glass is a solution of sodium silicate. Silicon is the element Kaolin, which is hydrated silicate, was absorbed and was found in lymph nodes. It produced no local reaction.

CONCLUSIONS

The application of asbestos to the surface of the heart brings about the development of new communications between one coronary artery and another.

It reduces the mortality following ligation of a coronary artery.

It reduces the size of the infarct that develops after a coronary artery has been ligated.

The application of asbestos to the surface of the heart is a safe surgical procedure in animals, provided a dosage of about 0.1 to 0.2 Gm. be used rather than larger doses.

Inflammatory agents used on the heart may not be without harmful side-effects, and they should not be used indiscriminately.

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STAB WOUND OF THE HEART

CASE REPORT OF SUCCESSFUL SUTURE

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THE FREQUENCY OF OCCURRENCE of stab wound of the heart at Harlem Hospital is revealed in the following tabulation of the number of admissions for this condition found in each 12 months of the five-year period from January 1, 1938, to August 1, 1942. There were 28 such cases recorded, five being admitted in 1938, ten in 1939, five in 1940, six in 1941, and two in 1942. Twenty-one of the total number of admissions were operated upon, and nine recovered. Seven died within one hour after admission and seven died during operation. Three of the above nine recoveries have been previously reported, two by one surgeon,³ and one by another.² The remainder were operated upon by four other surgeons.¹

So many operative successes can be attributed, in part, to the nature and extent of the injury to the heart and to the nature and extent of associated injuries. Other factors in this respect are the immediate recognition of the gravity of the injury and the necessity for early operative intervention. We have come to recognize the fact that extensive and serious damage to underlying structures all too frequently accompany the small surface laceration presenting an innocent appearance. Hence, a policy of exhaustive work-up and close clinical observation has been adopted in each case until the extent of the injury has been determined and the danger of mistaken diagnosis is eliminated.

Factors of importance in operative technic and in postoperative care, which directly influence success or failure, are the chief concern of the surgeon. They include the type of anesthesia, the kind and site of the incision for the approach to the pericardium, the management of the heart and mediastinum during the procedure, the closure of the incision and the indications for drainage, the close attention during the postoperative period to prevention of tension in the pleural cavity from fluid and from air, and the prevention of cardiac compression from fluid allowed to accumulate in the pericardial sac under tension.

The appended case report is that of the last patient in the above series.

Case Report—A well-nourished white male, age 25, was admitted to Harlem Hospital by ambulance, June 20, 1942, at 12 10 A M, having been stabbed in the chest during a holdup one hour previously. When first examined the patient was in shock, cold and clammy. Actively flowing dark red blood was issuing from a three-quarter-inch stab wound in the left chest in the sixth interspace at the outer border of the sternum. The patient was conscious, oriented, exceedingly pale, with a blood pressure of 60/40, and a fluttering pulse barely discernible at the wrist. A diagnosis of stab wound of the heart was made and the patient prepared for immediate operation. A

roentgenogram of the chest was taken on the way to the operating room, and an intravenous infusion of glucose 5% in saline 1000 cc was started. No other medication was given at this time. It is estimated that the operation was started approximately four and one-half hours after the injury.

Operation—Under ether anesthesia, a vertical incision was made over the left border of the distal two-thirds of the sternum down to the bone. A four-inch incision at right angles to this and extending outward over the fifth rib was then made, and about two inches of the fifth and sixth ribs were removed subperiosteally, together with their cartilages and a small portion of the outer border of the sternum. The pleural cavity was accidentally opened during this procedure. The collapsed and loosely-flapping lung was immediately grasped with a ring clamp, which was then allowed to hang over the edge of the wound. This procedure has been found desirable for combating the immediate effects of open pneumothorax. The pericardium was then opened vertically and several large blood clots were removed from the pericardial sac. Dark red blood spurted from the right ventricle with each systole and rapidly filled the pericardial sac. The bleeding points in the heart were seen to result from a through-and-through laceration of the right ventricle, *i.e.*, through the anterior wall into the chamber and out through the posterior wall, proceeding through the dome of the diaphragm at the base of the pericardial sac and, presumably, into the liver. The lacerations of the anterior and posterior walls measured approximately one centimeter in length. The crazily fluttering heart was grasped in the hand and steadied with a fixation suture of catgut through the apex of the heart. The wound in the anterior wall of the right ventricle was closed with interrupted No 0 chromic catgut. The wound in the posterior wall of the right ventricle was closed with the same type of suture in a similar manner. Active bleeding from the wound in the diaphragm was controlled with interrupted sutures of No 2 plain catgut. When the fixation catgut suture was removed from the apex of the heart muscle, blood spurted through the opening with each systole, making it necessary to apply several interrupted catgut sutures of No 0 chromic through the myocardium to effect complete hemostasis. The pleural cavity was then aspirated of all free blood and blood clots, and a stab wound was made through the seventh interspace in the midaxillary line for the purpose of drainage. A fenestrated one-quarter-inch rubber tube was passed through the stab wound to the costophrenic angle posteriorly, and was fastened in place by a silk suture to the skin, through a rubber cuff. A fixation suture of catgut through the margin of the lung at the interlobar fissure and to the parietal pleura at the line of the incision anchored the latter and aided in stabilizing the mediastinum. The transverse incision was then closed with No 2 chromic catgut through the parietal pleura, muscle and deep fascia. The pericardial sac was left open to drain into the pleural sac, and was not flushed with saline.⁴ The vertical incision was then closed with continuous catgut, so that the pleural cavity was rendered air-tight. Because of the proximity of the stab wound to the incisions, the wound was filled with sulfathiazole and the skin was not sutured. At the end of the operation the condition of the patient seemed good, except for fluid loss. Two hundred cubic centimeters of blood plasma from the blood bank was administered during operation, immediately followed by 800 cc of physiologic saline. Immediately postoperative the patient was placed in an oxygen tent. Arrangements had been made during this time for cross matching with a professional donor, so that within one hour after operation the patient was receiving a citrated whole blood transfusion.

Postoperative Course—During the postoperative period the patient was given sufficient sedation, at regular intervals, to overcome restlessness, excitement, and pain, so that he appeared comfortable at all times.¹ The thoracotomy tube was attached to a Cassasa¹ bottle for underwater drainage, and tested at frequent intervals for patency.¹ The thoracotomy tube was removed on the fourth day, and the wound healed completely.

two weeks later. Twelve hours after operation a blood transfusion of 500 cc was administered, and fluid balance maintained by continuous drip infusion of 5% glucose in physiologic saline. Chemotherapy by mouth was not employed, the temperature ranging from 100° to 102° F until the fourteenth postoperative day, when it receded to 99° F, then fluctuated to 101° F until the twenty-first day, after which it remained normal. The patient was kept in the oxygen tent for approximately two weeks. Roentgenograms of the chest on the eighth postoperative day showed clouding at the left base. The trachea had shifted to the right. An electrocardiogram, taken 12 days after operation, showed: Atrial rate 95, Ventricular rate 95, L₁-R T elevated, Q present, L-R T depressed. P-R interval 0.16 seconds, Q R S interval 0.08 seconds. Elevation of the R T segments denotes early change following pericardial injury.

The left lung filled out rapidly, and respirations became deeper. About three weeks after operation thoracentesis of the left chest posteriorly yielded 55 cc of sero-sanguineous fluid. The patient was allowed out of bed 30 days after operation, and was discharged on the thirty-fourth day. When last examined December 20, 1942, he was apparently quite well.

COMMENT—A choice of incision for transthoracic approach to the pericardium and heart is based upon (1) The rapidity and ease of adequate exposure for rib resection and exposure of the pericardium and heart. (2) The rapidity and effectiveness of air-tight closure. For this purpose a vertical incision downward at the lateral border of the sternum, then curved outward over the fifth rib, permits easy access for removal of the fourth and fifth ribs, as well as the formation of a skin flap that permits air-tight closure at the end of the operation.⁴ The T-shaped incision employed in this instance necessitates the raising of two flaps outward to expose the ribs but permits a greater exposure of the pericardium and heart with better visualization of the base of the pericardium and dome of the diaphragm beneath. Its cosmetic after-appearance compares less favorably.

This experience of passing a suture through the apex of the heart for stabilization demonstrates such a procedure to be unnecessary and harmful. The edges of the laceration in the myocardium can be brought together effectively to accomplish suitable closure if they are approximated with Allis' clamps, provided the latter are held gently and without traction. Such a procedure will avoid the necessity of closing the puncture wound made by a fixation suture through the myocardium. The edges of the incised pericardium were not sutured. Bleeding from these edges appeared insufficient to warrant the added procedure of suturing for control of possible hemorrhage after the blood pressure has risen. Complete and thorough removal of all blood clots and free fluid blood from both the pericardial and pleural sacs by suction is essential to lowered morbidity. The pericardial sac must be left open for drainage into the pleural sac so that collection of pericardial fluid to the point of incurring danger of cardiac compression, with its fatal sequence, will be prevented.⁴ The amount of drainage from the pleural cavity for the first few days postoperatively is sufficient to warrant the routine use of the thoracotomy tube through a separate stab wound in the axilla. Aspiration of accumulated fluid and control of tension pneumothorax requires careful

attention to their occurrence, so that immediate relief can be obtained by thoracentesis

It appears essential, postoperatively, to maintain as complete relaxation and comfort of the patient as possible and to provide sufficient free oxygen to offset the loss sustained by reason of the collapsed left lung¹ The need for oxygen administration decreases as the collapsed lung expands and sufficient time has elapsed for the myocardium to heal Stabilization of the mediastinum in the presence of sudden pneumothorax is easily accomplished by grasping the lung margin with a ring clamp¹ This is then allowed to hang over the edge of the wound while the operation is in progress and, when completed, the two lobes of the lung are fixed to each other and then to the parietal pleura by suture

Fluid loss must be overcome by immediate administration of plasma, whole blood transfusion or physiologic saline administered parenterally, as soon as the bleeding points are controlled

Fine chromic catgut for suturing the myocardium appears to be as effective as silk and obviates the introduction of nonabsorbable material

Allowing the skin edges to remain open and suffusing the tissues with sulfonamide compounds appears unnecessary Experience with immediate closure has demonstrated that the wound heals *per primam*

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THE SURGICAL MANAGEMENT OF SOLITARY CYSTS, OR CYST-LIKE STRUCTURES, OF PULMONARY ORIGIN

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THE TERMINOLOGY dealing with cyst-like structures of the lung is very much confused and the etiology of this condition, particularly as to whether congenital or acquired, has been under considerable controversy. It is our purpose to present six cases that have come under our observation because of certain accidents which occurred due to the presence of a cyst-like structure in the lung, or derived from lung tissue, and to discuss the surgical measures which were employed in dealing with these complications. In some instances the congenital nature of the cyst was obvious, in others it was open to question, and here the controversial nature of the lesion is discussed. One additional case is mentioned where a pulmonary cyst was present which has never given rise to symptoms.

The first account of a case of pulmonary cystic disease in the American literature was an autopsy study made by Koontz,¹ in 1925. This author collected 108 cases from other countries. The next year, Miller² reported the clinical course of an infant who died of a ruptured pulmonary cyst. Since this time there have been many papers dealing with all aspects of this abnormality, the most complete account of the whole subject being the monograph of Sellors,³ published in 1938, based on a study of 32 cases. This author collected over 400 cases in the literature including both solitary and multiple varieties. He points out that this figure is an entirely inadequate expression of the incidence of the disease and that, though uncommon, pulmonary cysts are certainly not a "medical curiosity."

Solitary cysts of pulmonary origin usually present themselves for treatment because of some accident to the cyst, such as infection or alteration of the mechanical air-exchange through a connecting bronchus. Both of these accidents may be further complicated by rupture. Quite frequently the fact that a cyst, or cyst-like structure, underlies the pulmonary disease is not at first recognized due to the fact that empyema, tension pneumothorax or a combination of the two masks its presence. Not infrequently a mistaken diagnosis of lung abscess is made when a solitary cyst becomes infected. In these cases, as pointed out by Sellors,⁴ the final differentiation rests with the pathologist. Once the underlying condition has been made clear, removal of the cyst, the cyst-bearing lobe, or an entire lung may be required properly to deal with the condition. Before this can be accomplished, however, it may be necessary to treat an empyema or "lung abscess" until the infection has been cleared up.

All of the six cases to be reported came for treatment because of some

accident to the cyst. It is interesting to note that in only three of the cases was a positive diagnosis of cyst made when the case was first seen. There were nearly as many types of complications as there were cases. These complications were: Infection of the cyst without rupture, infection of the cyst with rupture and the formation of pyopneumothorax, progressive expansion of the cyst after the subsidence of infection, rupture of the cyst without infection but with the presence of a ball-valve and the formation of a tension pneumothorax, and rupture of the cyst with the discharge of sterile fluid into the pleural cavity.



FIG 1.—Case 1. Appearance of chest on admission. The cystic cavity contains fluid and residual lipiodol.

CASE REPORTS

Case 1.—The first case* is that of a female, age 18, who was admitted to the Mary Hitchcock Memorial Hospital in January, 1937, with a history of having had several attacks of pneumonia in infancy, each one leaving her with increased cough, so that since the last attack of pneumonia, at the age of 12, she had raised from 100 to 150 cc a day of yellow, foul sputum. There was also occasional hemoptysis. Shortly before admission, a routine roentgenogram taken at the patient's school revealed a lesion of the right lung. She was then sent to a neighboring tuberculosis sanatorium where lipiodol bronchograms were taken. Following this the patient became acutely ill with increased cough, fever and sweating. She lost considerable weight and for some days before admission had been unable to lie flat in bed because of aggravation of her cough in this position.

A roentgenogram of the chest taken on admission is shown in Figure 1. This demonstrates that the cystic cavity is half filled with fluid and in the bottom there is

* Previously reported in the *New England Jour of Med*, 222, 579-584, 1940.

a small amount of residual lipiodol. After nine days of postural drainage, roentgenograms showed complete emptying of the cystic cavity (Fig. 2).

In view of the large size of the cyst and the long duration of the history, it was thought likely that it was of congenital origin and was probably lined with epithelium. Therefore, drainage, either by open thoracotomy or catheter, was thought out of the question, and either enucleation of the cyst or lobectomy was considered the treatment of choice. Therefore, on February 16, 1937, exploratory thoracotomy was performed, and it was found that the cyst was so deeply embedded in the upper lobe that it was necessary to remove the lobe in order to get rid of the cyst. Due to dense adhesions



FIG. 2.—Case 1. Lateral view after a short term of postural drainage.

in the lower part of the chest the presence or absence of a middle lobe was not proven, though it was observed that the cyst had a single bronchial communication arising from the upper lobe bronchus as a separate branch. The cyst was opened during the process of removal and, in spite of this, the chest was closed without drainage.

Following operation the patient developed a pure hemolytic streptococcic empyema, and, on February 23, 1937, treatment was begun with "red prontosil," given intramuscularly and directly into the empyema cavity. In five days the cultures were sterile from the pleural cavity and medication was discontinued. The temperature immediately returned to normal after discontinuance of the prontosil, and the patient made an uneventful recovery. The gross specimen is shown in Figure 3.

On examination, the cyst contained all the structures of a bronchus, since its lining consisted of flattened bronchial epithelium and the wall itself contained cartilage. The lung tissue surrounding the cyst showed no changes except for an increase in interstitial tissue in some areas.

The lower lobes failed to overexpand sufficiently to occupy the space left by removal of the upper lobe, and one year later the patient entered the hospital with a return of empyema in this space. This time there was a mixture of organisms and there was subcutaneous emphysema under the tissues of the back due to a bronchial fistula. The cavity was drained through the old incision, resulting in prompt recovery from the empyema, and then a posterior thoracoplasty, removing segments of the first five ribs, was performed in one stage. This resulted in complete recovery. The patient has no cough or sputum, has since been married and has been delivered of a healthy baby without ill effects.



FIG. 3—Case 1. Specimen removed at operation consisting of the right upper lobe and cyst.

SUMMARY A six-year follow-up has been obtained on this case following right upper lobectomy for an infected cyst, the congenital nature of which can hardly be questioned. There was failure of the other lobes to overexpand and fill the upper lobe space, and, one year after lobectomy, a bronchopleural fistula and a mixed empyema developed in this space. These complications were successfully treated by intercostal drainage and upper thoracoplasty. It is noteworthy that this patient had had pulmonary symptoms since childhood.

Case 2—The second case* was almost identical to the first. This patient was a college boy, age 18, who was first seen in October, 1938. He was known to have had a lung cyst since the age of 13. This was discovered in a routine roentgenogram at school in 1933 (Fig 4†). Subsequent films were secured at intervals, one of which, taken in 1937 (Fig 5), shows the cyst to be empty at that time. The cyst was said to have disappeared at the age of 17. He, however, always had a chronic productive cough which was aggravated by exertion. Two years prior to entering college he had an attack of pleurisy which kept him in bed a week. He never had hemoptysis.



FIG 4—Case 2. Appearance of the lungs in 1933, when the patient was 13 years old.

When the boy entered college a routine roentgenogram of the chest was taken showing a large thin-walled, sharply defined cavity in the anteromedial portion of the right lung (Fig 6). The cyst at this time showed a fluid level. He seemed somewhat under par physically, and was easily fatigued. In view of these facts, together with the hazard of harboring such a potentially dangerous lesion, operation was advised. As his home was in Boston, he was referred to Dr. Churchill of the Massachusetts General Hospital.

* Dr. Edward D. Churchill, of Boston, kindly supplied some of the photographs and clinical data on this case.

† We are indebted to the Massachusetts Department of Public Health for the roentgenograms reproduced in Figures 4 and 5.

He entered the Massachusetts General Hospital, June 26, 1939, where examination of the sputum was negative for tubercule bacilli and *Beta* hemolytic streptococci. Operation was performed, June 29, 1939, and Dr Churchill was able to dissect the cyst free from the upper lobe without damaging the lobe (Fig 7). The patient's postoperative course was complicated by the presence of an empyema which required rib resection, but after this his condition rapidly picked up and he was able to finish his college course successfully.

The clinical findings here are compatible with the diagnosis of congenital lung cyst, though the details of the pathologic examination are not at hand.

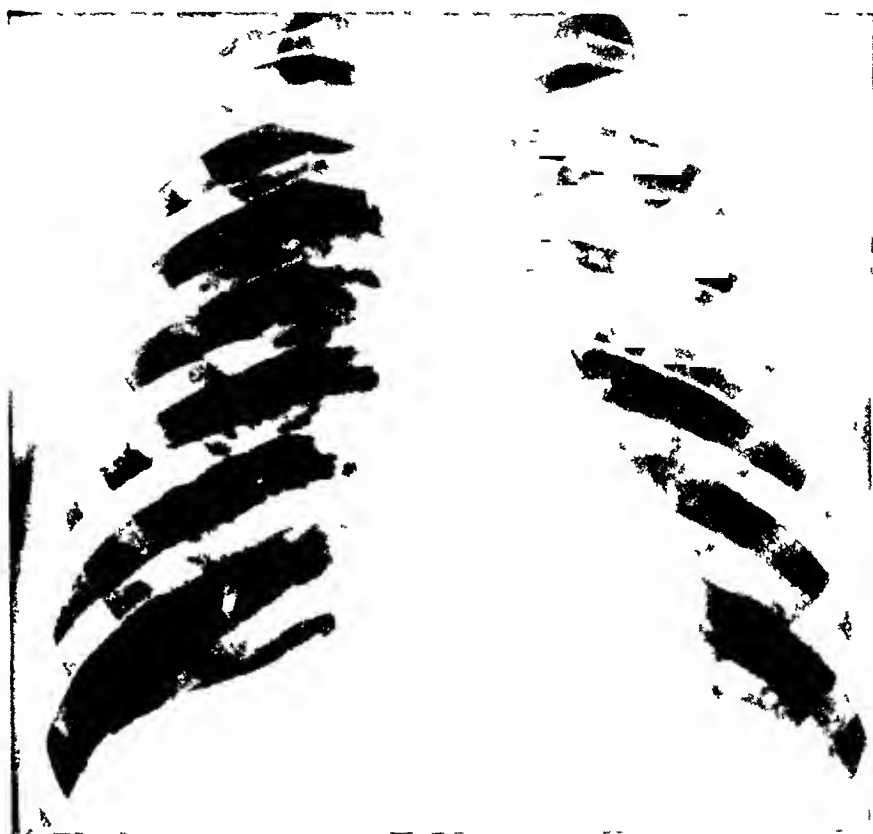


FIG 5—Case 2. The cyst now empty. Roentgenogram taken in 1937, when the patient was 17 years old.

SUMMARY A three and one-half-year postoperative follow-up of this case has been obtained. The patient had a congenital cyst of the right upper lobe with chronic infection and recurrent episodes of acute infection. He made a complete recovery after enucleation of the cyst and subsequent rib resection. A lung cyst was demonstrated in this case roentgenologically, six years before operation. Intermittent pulmonary symptoms had existed since childhood.

Case 3—This case represents rupture of a cyst causing pyopneumothorax, which occurred in a baby, age three months, who was admitted to the Mary Hitchcock Memorial Hospital for the first time in April, 1941. The baby was very well until ten days prior to admission, at which time she had what was considered to be a gastrointestinal upset, characterized by anorexia, constipation and distension of the abdomen. This cleared up after two or three days but she began to cough and a low-grade

fever was present. One day before admission she began to have paroxysmal attacks of gasping respiration. These attacks were relieved somewhat by propping the baby up on a pillow. On the day of admission there was the sudden onset of gasping respiration, worse than before, and progressive. She was rushed to the hospital *in extremis*, gasping for breath and cyanotic. A roentgenogram taken immediately is shown in Figure 8. It was thought that a spontaneous tension pneumothorax was



FIG 6—Case 2. A lateral view just before operation in 1939.

present, of unknown etiology, though it is interesting to note the clear area over the spine at the base of the right lung field. At once, a needle was inserted in the right pleural cavity and connected with a pneumothorax machine. The pressure was so great that the water was forced out of the monometer and no accurate measurement could be taken. Aspiration of the air was commenced then by syringe, and after considerable amounts had been removed the patient's condition improved. Further aspiration at this time resulted in the withdrawal of thick pus from the right pleural cavity which, on culture, was found to contain pure *Staphylococcus aureus*. The patient's condition was improved by the immediate emergency treatment. Another roentgenogram immediately after the first tap is shown in Figure 9, and demonstrates two definite air pockets. A transfusion was administered because of a rather severe anemia and sulfathiazole was begun.

Several subsequent chest taps were made, which resulted in the withdrawal of thick pus, which always showed a culture of *Staphylococcus aureus*. A later roentgenogram (Fig 10) demonstrated a definite pyopneumothorax, and as this condition

was gradually relieved the cystic shadow in the right midlung fields persisted. After three weeks it was no longer possible to aspirate pus from the pleural cavity and roentgenograms failed to show the presence of any residual empyema.

The patient continued to have respirations which were always above 50 per minute, and usually were around 60 occasionally going up as high as 80 or 90. Expansion of the cyst (Fig 11) was noted with alarm, since it was thought that another rupture might occur at any time. On one occasion the cyst was aspirated with a needle and syringe and it was found that air was under considerable pressure within the cyst. Following aspiration the cyst was diminished in size, but in 24 hours had increased to its previous dimensions.

In view of the continued elevation of respirations and the progressive expansion of the cyst, it was decided to operate upon the patient, with a view to removing the cyst. An exploratory thoracotomy was performed, July 25, 1941, when the baby was six months old. It was found that the cyst was an extremely thin-walled one, situated between the middle and lower lobes, and densely adherent to both. It was impossible to remove the cyst intact because of the thinness of its walls and the denseness of the adhesions to the surrounding normal lung. It was dissected free piecemeal, and a definite bronchial communication was observed at the hilum. Two silk ligatures were placed around the neck of the cyst close to the hilum and the cyst was cut away. There was practically no evidence of the previous empyema except for avascular adhesions binding the upper and middle lobes to the chest wall, in which was an occasional bit of yellow, grumous material. A Pezzar catheter was placed in the pleural cavity. Immediately upon returning the patient to bed, this was connected with a constant suction apparatus. For the first two or three hours there was difficulty in withdrawing air fast enough by this means apparently due to a leak through the incision in the chest wall. This sealed off, however, and from here on the patient's convalescence was only complicated by slight difficulty in maintaining the normal chemical balance for the first week postoperatively.

This undoubtedly represents a congenital cyst. The age of the patient would favor this diagnosis together with the demonstration at operation of a definite bronchial communication. Microscopically, the pieces of cyst submitted for examination revealed small areas of cartilage in the wall and there was one area on the inner surface lined by cuboidal epithelium.

From the location of the cyst in the chest the possibility arises of its having been a cystic accessory lobe. All three normal lobes were accounted for on the right and



FIG 7—Case 2. The surgical specimen was removed by Dr. Churchill, without damage to the lobe.

the cyst seemed to be independent of all three except for vascular adhesions between it and the adjacent middle and lower lobes

SUMMARY A one and one-half-year follow-up has been obtained on this patient, who, at the age of three months, sustained a rupture of a congenital pulmonary cyst on the right side. This resulted in a pyopneumothorax and marked mediastinal shift. The air was immediately aspirated and the empyema cleared up with repeated aspirations and the administration of



FIG 8—Case 3. Chest roentgenogram on admission. There is extreme mediastinal shift. The irregular clear area over the spine just above the diaphragm later proved to be a cyst.

sulfonamides. The cyst then began to balloon up again, and reached huge proportions. When the patient was six months of age the cyst was removed surgically. There is strong evidence in support of the lesion being a cystic accessory lobe.

Case 4—The following case is one which showed both infection and mechanical difficulties with bronchial air-exchange. The patient was a female, age 36, who was admitted to the hospital, November 24, 1940, with an illness which began six weeks before entry. At that time she began work in a house which was improperly heated, and two or three days after starting work, she became acutely ill, with high fever, diarrhea and soreness of the mouth. Shortly afterwards she developed soreness in the back and extremities, became progressively weaker, and had frequent attacks of sweating. There were no chills. She was taken to a neighboring hospital where, in a few days, the fever subsided somewhat and the soreness of her muscles disappeared. Her strength began to return over a period of two or three weeks, while still in the hospital, until one week prior to entry, when she began to have a paroxysmal cough and afternoon fever. There was also occasional vomiting.

PULMONARY CYSTS

The sputum resembled saliva, and there was no hemoptysis. During this time, also, there was pain in the right upper anterior chest, made worse by coughing and deep breathing.

On admission, the patient appeared acutely ill. Temperature 103° F, pulse 140, respirations 30. Except for emaciation the positive findings were related to the chest. There was tenderness over the right upper anterior portion and diminished resonance over this area. Auscultation revealed diminished breath sounds in front, extending around to the axilla and numerous moist râles were present. Examination of the rest of the lung fields was essentially normal. One of the roentgenograms of the chest taken on admission is shown in Figure 12.



FIG 9—Case 3. Picture taken on the same day as Figure 7, after withdrawing air and pus. The cystic cavity is now well outlined.

The diagnosis of lung abscess was made and it was supposed that this resulted from an earlier pneumonia. Conservative treatment was followed, consisting of postural drainage, bronchoscopic aspiration once a week, and sulfonamide therapy. Several transfusions were administered.

Under this regimen the patient began to improve, and at the end of three weeks her temperature returned to normal where it remained. Her weight, which was not obtained on admission because of the patient's condition, was 92 pounds after she had been in the hospital 17 days. Her weight began to increase during the fifth week of hospital stay, and at the end of 74 days it had reached 101 pounds. The sputum, which on admission amounted to 60 to 90 cc a day, rose to 240 to 300 cc as soon as postural drainage was started. During the third week, when the temperature returned to normal, the sputum also dropped to a daily average of 30 to 60 cc.

In January, 1941, after the patient had been in the hospital approximately seven weeks, roentgenologic examination showed a remarkable change in the appearance of the "abscess." As shown in Figure 13, the cavity in the lung was now entirely free of surrounding infiltration, had a very thin wall, and no longer contained fluid. Subsequent examination, two weeks later, as shown in Figure 14, demonstrated an increase in diameter of the cavity.

Possibly the patient had had an infected solitary pulmonary cyst all along, the infection had cleared up, but there was a ball-valve action in the connecting bronchus, with subsequent distension of the cyst. In favor of this hypothesis was the absence



FIG 10.—Case 3. Roentgenogram nine days after admission showing a pyopneumothorax persisting and the cyst essentially unchanged.

of surrounding pulmonary fibrosis. On the other hand, it is entirely possible that this condition did represent an abscess wherein the infection had cleared and then the bronchus had become partially occluded, resulting in progressive distension of the abscess cavity. There is no clear-cut differentiation between the two conditions in this instance. The importance of the differentiation would be to know whether or not the cyst was lined by epithelium and if the walls contained cartilage. If these were not present, closure could be obtained with drainage, either by open thoracotomy or closed drainage, with a catheter, as pointed out recently by Majer.⁵ However, biopsy of the cyst would be necessary to determine this point, and this in itself would require a major operation and drainage would require a two-stage procedure to guard against the development of empyema. Furthermore, biopsy of one portion of the cyst wall would not guarantee a knowledge of the condition of the entire lesion. Therefore, removal of the cyst was decided upon, and, since at this point the patient's condition seemed favorable, operation was performed, February 6, 1941.

A posterolateral incision was made, the scapula was partially mobilized and re-

PULMONARY CYSTS

tracted upward, the fifth rib was widely resected and the pleural cavity opened in the bed of this rib. The cyst of the upper lobe was immediately apparent, lying anteriorly and deeply embedded in the lobe. Where the cyst approached the surface of the lung there were dense avascular adhesions. The mediastinal aspect of the lobe was adherent also and the pleural cavity was obliterated over the apex by delicate avascular adhesions. The lower lobe was entirely free and there was no middle lobe present. The cyst failed to collapse with the rest of the lobe when intratracheal pressure was diminished, and firm pressure on the cyst with the hand failed to express any air. It was impossible to remove the cyst separately from the lobe and in order to remove



FIG. 11—Case 3. Three weeks later the empyema has cleared up, but the cyst has expanded to an alarming degree.

the lobe without damaging the cyst, a separate ligation of the upper lobe vessels at the hilum was done. A tourniquet was applied to control the escape of air from the bronchus before the lobe was amputated close to the hilum. A small amount of remaining lung tissue was sutured over the upper lobe bronchus with catgut. The incision was closed without drainage.

The pathologists have not been able to demonstrate a definite bronchial communication with the cyst on gross inspection (Figs. 15 and 16). Microscopically the wall of the cyst was composed of dense, fibrous tissue in which no cartilage was observed. The lining was devoid of epithelium though it is only fair to state that the cavity was stuffed with cotton before fixation, which could easily have completely denuded a delicate epithelial membrane. Certainly, the necessary and sufficient findings to enable a diagnosis of lung cyst to be made are lacking in this instance and it is probable that lung abscess was the basic lesion.

The patient stood the operative procedure very well and made an entirely uneventful convalescence. Her temperature rose to 101° F for five days following operation, and then rapidly declined to normal. The lower lobe overexpanded promptly to fill the right thoracic cage except for a small area at the apex which was filled with sterile fluid.

This patient has been followed regularly in the Out-Patient Department and is entirely normal as far as pulmonary symptomatology is concerned. There is still a cap of density over the apex of the right hemithorax, but the patient has no cough and no chest pain, and is able to keep on with her house work.

SUMMARY A two-year follow-up has been obtained in this case which exhibited the findings of either lung abscess or infected lung cyst with



FIG 12—Case 4 Chest roentgenogram on admission, when a diagnosis of lung abscess was made

progressive ballooning of the cavity. A right upper lobectomy was performed, and the pathologic findings are more in accord with a diagnosis of lung abscess than of cyst. The absence of pulmonary symptomatology prior to the onset of the present illness is against but does not rule out a preexisting cyst.

Case 5—This case* is characterized by multiple attacks of spontaneous pneumothorax caused by the rupture of a cyst-like structure on the surface of the lung, probably representing an emphysematous bulla.

The patient was a male meat-cutter, age 30, who was first seen March 30, 1936. Two years previously, he had experienced a sudden onset of pain in both sides of the chest and dyspnea. No roentgenograms were taken. The patient gradually improved.

* Previously reported in the Jour Thoracic Surg, 10, No 5, 566-571, 1941

PULMONARY CYSTS

and was able to return to work in about two months. A burning, cramping sensation in the right side of the chest persisted for some time. About one year later, he again had a sudden attack of dyspnea and pain, similar to the first. A roentgenogram of the chest, at another hospital, revealed a complete right pneumothorax, with a cyst-like structure projecting beyond the border of the collapsed lung. The symptoms improved rapidly, and the patient returned to work in a week. Three weeks later, he had a third attack and for some time subsequent to this his physician withdrew air at intervals from his right chest. The third attack lasted four weeks. His symptoms gradually disappeared and he remained well until the middle of March, 1936, when he suffered



FIG 13—Case 4. Five weeks after admission, the clinical and roentgenologic evidence of infection are gone and a cystic shadow remains.

a fourth attack of right-sided chest pain and dyspnea. He was in bed for two weeks, with only partial relief of symptoms. At this time (March 30, 1936) he was referred to the Mary Hitchcock Memorial Hospital.

On admission, the patient presented a picture of extreme dyspnea and cyanosis, with shallow, rapid respirations and weak, thready pulse. The temperature was normal. Physical examination revealed the signs of a right pneumothorax; roentgenograms showed a right tension pneumothorax (Fig 17). The patient's acute symptoms were relieved by aspiration of air from the right pleural cavity, but repeated aspirations were necessary in order to keep the dyspnea under control. Because it was felt that the adhesions, shown in the roentgenograms, might play some part in preventing closure of the perforation in the lung, thoracoscopy was performed, April 11, 1936, and a cautery pneumonolysis was done, severing the adhesions. Subsequent to this procedure, the patient's condition showed progressive improvement and the lung partially reexpanded. It was at this time that the large bleb on the right upper lobe was first noted (Fig 18). The patient was so much improved symptomatically that

he refused to remain in the hospital, and was discharged against advice, April 24, 1936

He returned to work and felt well until May 15, 1936, when he had a fifth attack, characterized by dyspnea and cyanosis. He was admitted to the hospital, May 16, 1936, in essentially the same condition as on the first admission, except that the symptoms were somewhat less severe. The roentgenogram taken at this time showed a right pneumothorax. Another adhesion had formed.

The emphysematous bleb was considered to be the cause of the pneumothorax, and excision of this lesion was proposed. Justification for this procedure was based on the fact that the frequent recurrences were handicapping the patient and, also, at least one of the attacks had produced a tension pneumothorax of such alarming proportions that his life was in danger.



FIG 14—Case 4. A roentgenogram taken two weeks after Figure 13 shows that the cyst has almost doubled in size.

Operation was performed, May 23, 1936, under intratracheal gas-oxygen-ether anesthesia. A right parascapular incision was made, and the fifth rib was resected. The pleura was incised in the rib bed. A bleb, measuring approximately five centimeters in diameter, was seen on the lateral aspect of the apex of the upper lobe. A broad adhesion extended from the medial aspect and apex of the cyst to the mediastinum. There was a charred area on this adhesion from previous cauterization. There were some adhesions between the middle upper and lower lobes and some between the lower lobe and the chest wall. The pleural surfaces were otherwise normal in appearance.

The adhesion to the cyst was cut away and hemostasis secured. The apex of the cyst was grasped with forceps, and a purse-string suture was placed in the thickened pleura around the base of the cyst. The suture was drawn tight and the bleb removed.

PULMONARY CYSTS

The cut surface was sewed over, and the incision in the chest wall was closed without drainage

The pathologic report was as follows "Study of numerous sections reveals no definitely identifiable lung substance. The only feature suggesting the association of this specimen with the lung is the presence of a great many macrophages filled with black carbon-like pigment. Elastic tissue stains reveal a very small amount of elastic tissue but none in any position to suggest alveolar arrangement. No bronchial structures are seen. Two types of surface are seen in the section, one, which is interpreted as being the original pleural surface has underlying it a broad band of dense hyalinized fibrous tissue. No covering is apparent, and there is no infiltration of this region.

FIG 15



FIG 16

FIG 15—Case 4. The cystic structure is still under tension, though the rest of the upper lobe has collapsed.
FIG 16—Case 4. Section of the cyst shows a smooth lining. No bronchial opening is demonstrated.

Opposite this surface is one which bears a small amount of inflammatory exudate in spots. Adjacent to this surface there is abundant infiltration by eosinophils, and a few polymorphonuclear leukocytes and scattered small accumulations of lymphocytes. There are some small arteries which are occluded. Vascular channels are numerous, and there are some brown, pigment-filled phagocytes, suggesting that there has been hemorrhage into the tissues."

Evidence, therefore, is lacking in this case in support of a definite congenital cyst. It probably represents an emphysematous bulla, of the type described by Kjaergaard⁶

Postoperatively, the patient ran an oral temperature reaching about 100° F daily for two weeks. The pulse was about 120 for three days and then leveled off to 100, dropping to normal with the temperature two weeks after operation. Respirations were not increased.

During this period there was some mucopurulent sputum. Fluid accumulated in the right pleural cavity, and thoracenteses yielded 350 and 300 cc., respectively, on the 6th and 9th postoperative days. The fluid was serosanguineous, and was sterile on culture.

The patient gradually improved, and was discharged, July 1, 1936. He resumed activities and returned to work. He has now been working seven years as a clerk in a grocery store, with no symptoms or ill effects.



FIG 17—Case 5. Roentgenogram taken on admission. There is tension pneumothorax, with extreme mediastinal shift.

SUMMARY A seven-year follow-up has been obtained in this case, who had five attacks of spontaneous pneumothorax from rupture of a subpleural cyst-like structure. On at least one occasion a high degree of tension pneumothorax was present. The cyst-like structure was excised and the patient has remained well since. Pathologic criteria are lacking for a satisfactory diagnosis of cyst, and it is thought likely that the lesion was an emphysematous bulla.

Case 6—When first seen for a pulmonary complaint, R. S. was age 24, and was admitted to the hospital, July 15, 1937, with a diagnosis of bronchopneumonia. Routine roentgenograms of the chest demonstrated a small area of acute pulmonary infection in the right costophrenic angle. Also, at this time it was discovered that there was a dense, smoothly-outlined, oval shadow in the left upper lung field (Fig 19). The patient recovered from the bronchopneumonia promptly, but failed to return for further study of the shadow in the left upper lung field.

PULMONARY CYSTS

He was readmitted in November, 1939, acutely ill and complaining of severe left chest pain, cough and fever. Roentgenograms taken at this time are shown in Figures 20 and 21, and demonstrate a tremendous increase in the size of the previously discovered shadow. While exploratory operation or aspiration of this cystic shadow was being contemplated, the patient had a sudden exacerbation of thoracic pain, became quite cyanotic and breathless. This was soon followed by a diminution of pain in the chest. A roentgenogram (Fig 22) showed that the cyst had ruptured into the pleural cavity. Thoracentesis at this time recovered 300 cc of cloudy, thin, yellow



FIG 18—Case 5. Partial reexpansion after repeated thoracentesis. The cystic shadow in the upper lobe area is demonstrated.

fluid. Smear and culture were negative for organisms but showed many white cells, most of which were polymorphonuclear leukocytes. Following this episode the patient quickly recovered, his pain disappeared, the temperature returned to normal and he was discharged, after a hospital stay of 12 days.

He returned for operation, June 9, 1940, seven months after his previous admission, and at this time it was seen roentgenologically (Fig 23) that the cystic shadow had returned to its original size and contour. It is interesting to note in these films an area of increased density at the base of the cystic shadow. Operation was performed June 21, 1940. The left pleural cavity was opened through a posterolateral incision, with resection of the sixth rib. After freeing up a few avascular adhesions, the cyst was easily located protruding through the surface of the upper lobe. It was adherent at its apex to the posterolateral chest wall, and apparently deeply embedded in the lobe. It was possible, however, to develop a cleavage plane between the lung and the cyst, and this progressed without encountering large blood vessels or bronchi. The upper lobe and cyst were completely separated and it was then found that the base of the

cyst was adherent to the arch of the aorta just distal to the left subclavian artery. The cyst was rather thick-walled, and at the base, where it was straddling the aorta, there was a hard mass within the cyst wall. The base was removed from the arch of the aorta without difficulty, complete hemostasis was secured, and the chest was closed without drainage.

The pathologic findings indicate that the specimen represents a cyst of a rudimentary accessory or aberrant lung lobe. The hard area at the base of cyst was found to be a well-formed bronchus, about one centimeter in diameter (Fig 24). The walls



FIG 19—Case 6. Roentgenogram taken on admission demonstrates the sharply defined lesion in the left upper lung field. The area of increased density at the base of the lesion should be noted.

contained typical cartilage, and the lining was composed of tall, columnar, ciliated epithelium. The bronchial lumen communicated directly with the main cyst cavity, which measured 7.5 cm in greatest diameter. The cyst also was lined with columnar, ciliated epithelium.

It is rather difficult to reconstruct the life history of this lesion. The patient had had numerous hospitalizations, here and elsewhere, and no pulmonary lesion had been discovered, to our knowledge. Perhaps originally the rudimentary bronchus was all that existed and, as time went on, the accumulated secretions from the lining epithelium caused a gradual distension of the blind end of the bronchus to form the cyst. The final rapid distension and rupture may have been accounted for by stimulation of the glandular secretion by adjacent or intrinsic infection from which the bacteria had disappeared by the time the cyst ruptured. Examples of similar lesions are infrequent in the literature but disease of aberrant lung tissue was discussed by Freedlander and Gebauer,⁷ in 1938.

Convalescence was entirely uneventful. Thoracentesis was performed once, and

sterile, blood-tinged fluid was recovered. The lower lobe gradually expanded to occupy the entire left hemithorax. The patient has been followed at frequent intervals and is entirely free of pulmonary symptoms.

SUMMARY A two and one-half-year follow-up has been obtained in this case. The lesion represents a cyst of a rudimentary accessory lung lobe which gradually expanded over an unknown period of months or years, with final rupture into the pleural cavity. The fluid obtained was sterile. The cyst arose in the mediastinum and was embedded in the left upper lobe. A definite bronchus was present at the base of the lesion.



FIG. 20.—Case 6. Appearance of the chest two years and four months after the previous admission.

DISCUSSION

Of the six cases cited, four almost surely represent congenital cysts of pulmonary origin. Two of these (Cases 3 and 6) were cystic accessory lobes arising outside the normal lung tissue. The other two probably were not congenital cysts since one (Case 5) resembled an emphysematous bulla more closely than a true cyst and the other (Case 4) was probably originally a lung abscess, though there are certain findings which militate against this conclusion.

Since all of these cases presented themselves because of acute or subacute manifestations due to the presence of a cyst or cyst-like structure, it is interesting to speculate on the incidence of these structures occurring as silent lesions. A conclusion reached in this regard would help in deciding

the relative danger of ignoring such a lesion when accidentally discovered Singer⁸ states that symptomless cysts are not often seen, and believes they probably should not be operated upon Eloesser⁹ and Maier,¹⁰ also, are of this opinion, and the latter believes that many so-called upper lobe cysts are the result of infection and are not true cysts



FIG 21—Case 6 A lateral view shows the posterior position of the lesion

A review of the findings on routine roentgenograms taken on all members of the entering class at Dartmouth College reveals that in the five years between 1935 and 1942, 4,983 examinations were made. The diagnosis of solitary lung cyst was made once, and that is our Case 2. This could not be considered an accidental finding nor a silent lesion since the patient was known to have a cyst and it had been productive of symptoms for years. During the same years in the general hospital, 6,622 chest roentgenograms were taken, including retakes, and one unquestionable instance of an asymptomatic lung cyst was encountered.

This occurred in a woman age 56, who entered the hospital for removal



FIG 22—Case 6 The cystic lesion has ruptured into the pleural cavity



FIG 23—Case 6 Six months after rupture the cyst has resumed its original contour

of a toxic adenomatous thyroid The lateral chest roentgenogram is shown in Figure 25 The patient was an intelligent, educated woman, and had consulted her physician at regular intervals She had no knowledge of the existence of any lung lesion, and there was no history of pulmonary difficulties She had an uneventful convalescence from subtotal thyroidectomy, under local anesthesia, performed July 27, 1937, by Dr J P Bowler A letter

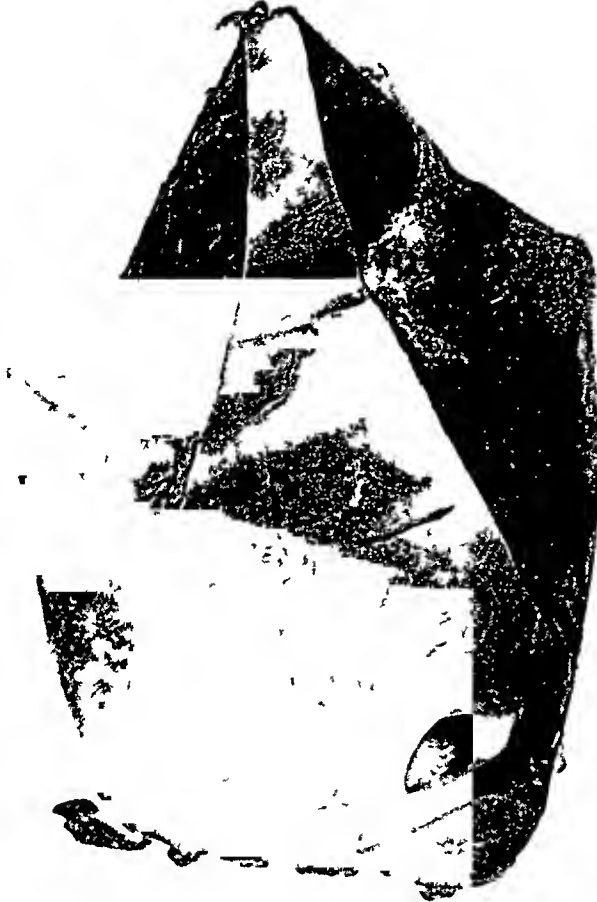


FIG 24—Case 6 The opened surgical specimen showing the well formed bronchial stump at the bottom of the cyst

received from her, dated June 25, 1942, states that she has been in perfect health since her hospital stay, and there have been no pulmonary symptoms of any kind

There was one other case which might be a pulmonary cyst, but the diagnosis is so uncertain that it is not included in the present report

From this small number of roentgenograms, and from accounts in the literature, as cited above, it would seem that asymptomatic cystic pulmonary lesions must be uncommon, but, in contrast to some other opinions, we feel that when they are observed removal should be advised if the patient's condition will permit The likelihood of accidents to the lesion is very

great, and once complications have occurred a serious situation may develop rapidly and, at best, an extremely eventful clinical course may readily ensue

Extirpation of the lesion, when possible, would seem to be the best method of treatment. If the lesion has an epithelial lining, collapse or simple drainage will not effect a permanent closure of the cavity (cf discussion under Case 4). The scope of the operation may vary from simple excision or enucleation of the lesion itself, as in three of the cases herewith reported,



FIG. 25—Case cited in Discussion. A thin walled cyst in the left anterior lung field, fluid level at bottom

or lobectomy, or even total pneumonectomy may be required (Gale,¹¹ Roberts,¹² and others). Three cases reported by Maier and Haight,¹³ were first treated as empyema by open drainage, but due to failure of cavity closure, later lobectomy in two cases, and enucleation in the third, were required for cure. Permanent closure of large balloon cysts by an endocutaneous flap is discussed by Brown and Block.¹⁴

The elimination of infection in the cavity insofar as possible is an important preoperative requirement. With a bronchial communication, postural drainage may accomplish this goal, but in closed cysts or where the communicating bronchus is inadequate due to its small diameter, or its position relative to the cavity, external drainage may be required as in the cases of Maier and Haight, cited above. Since the cyst contents or lining may harbor pathogenic

organisms even under the best circumstances, avoidance of opening the cyst during removal is desirable, but is an ideal not always possible of achievement. To remove the cyst intact, careful dissection and individual ligation of the hilar structures may be necessary. This technic was employed successfully in one of our cases (Case 4) and, if it had been utilized in Case 1, instead of the tourniquet technic, opening of the cyst, and possibly the following empyema, might have been avoided.

The employment of drainage after cyst removal is, of course, an individual problem and one that has to be settled at the time, but, in general, it is probably a safe maxim that, if the cyst has been opened during removal drainage should be instituted.

The postoperative care of this class of patient does not employ different management from that utilized after other open chest operations where there has been manipulation or actual resection of lung tissue. Prompt expansion of the remaining pulmonary tissue should be accomplished and maintained. Whether or not to increase the oxygen intake depends on the individual situation and may be unnecessary. The usual attention must be given to fluid intake and blood replacement. Even if no lung tissue is resected, there is usually an accumulation of serosanguineous fluid in the pleural cavity in the first 48 hours. If no drainage has been employed, aspiration of this fluid once or twice may be advisable, more for bacteriologic determination than relief of pressure. If there is no infection the fluid will absorb over a period of 10 to 14 days.

Complete restoration of the pulmonary function should be the rule, and has been accomplished in all of the cases reported in this article.

SUMMARY

Seven cases of solitary cystic lesions of pulmonary origin are reported. Six of these cases presented themselves for treatment because of various accidents incident to the presence of the cyst. All six were operated upon successfully (five by the author). The seventh case had a symptomless cyst and has not been operated upon. The incidence, diagnostic criteria, operative procedures and pathologic findings relating to these lesions are discussed.

CONCLUSIONS

- 1 Solitary cystic lesions are usually seen because of some accident to the cyst.
- 2 The cure of the condition is usually surgical and preferably involves extirpation of the cyst, which may require lobectomy or pneumonectomy.
- 3 The differentiation between congenital and acquired cysts prior to pathologic examination is often impossible.
- 4 Symptomless cysts are uncommon.
- 5 Even silent solitary cystic lesions should be removed if conditions permit.

The author wishes to express his thanks to the Thoracic Study Unit of the Hitchcock Hospital for their cooperation in caring for the cases reported in this article.

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THE SPREAD OF CARCINOMA OF THE RECTUM INVASION OF LYMPHATICS, VEINS AND NERVES*

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SINCE THE WORK OF HANDLEY,¹⁵ in 1910, much attention has been given to the lymphatic route of spread of carcinoma of the rectum. Many extensive and painstaking studies have been made into this feature of rectal carcinoma in order to determine the prognostic implications of nodal involvement and the direction of spread of the carcinoma. The anatomic descriptions of the rectal lymphatic channels by Delamere, Poirier and Cuneo⁹ paved the way for later studies. Early investigations by Miles,²² Monsarrat and Williams,²⁴ Cole,⁵ Cheate,⁴ Pennington,²⁹ and others, gave impetus to more exhaustive studies by McVay,²¹ one of us (Bargen²) and Larsen, Gabriel, Dukes and Bussey,¹² Gilchrist and David,¹³ Collier, and others,⁶ and Grinnell.¹⁴ These investigators, and the large numbers of cases studied by them, have emphasized the importance of the lymph nodes as prognostic indicators in rectal carcinoma, and around this pathologic feature of the disease have been centered the present methods of surgical treatment.

Venous invasion in rectal carcinoma has been observed for many years, Mayo,¹⁹ McArthur,²⁰ Smith,³⁰ Monsarrat and Williams,²⁴ and Miles²³ noting this feature and commenting on it. During the past four years, increasing attention has been given to venous invasion of rectal carcinoma as its clinical and prognostic importance has been seen to grow. The frequent development of visceral metastatic lesions after radical resection of the rectum for carcinoma has stimulated interest in this phase of invasion by carcinoma.

Brown and Warren,³ in one of the first reports during the present period of interest, expressed the opinion that the lymph nodes have been poor indicators of visceral metastatic lesions, which are often present independently of neoplastic nodes. They found that 31 per cent of patients without nodal involvement by carcinoma had visceral metastatic lesions, and they maintained that the spread of rectal carcinoma through the blood vessels is at least as important as by the lymphatic route, and that evidence of this spread is usually available in the primary growth. In the prediction of visceral metastatic lesions from the primary growth, the presence of intra-vascular invasion means as much from the prognostic standpoint as neoplastic nodes, and its absence means much more.

* Abridgment of thesis submitted by Dr Seefeld to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M S in Surgery

Dukes and Bussey found that in 16.6 per cent of 699 specimens of rectal carcinoma the veins were invaded and demonstrated small carcinomatous implants along the superior hemorrhoidal vessels.

Grinnell recently found veins involved in 36 per cent of 75 cases studied. In 90 per cent of 30 cases in which there were visceral metastatic lesions, venous invasion was demonstrated in the primary growth. Twenty-five per cent of the patients who had visceral metastatic lesions failed to show nodal involvement.

The first reported instance of neoplastic invasion of nerves was probably that of Cruveilhier,⁸ in 1842, but this phenomenon has been encountered frequently since then, and almost all types of neoplasm have been observed to use the perineural spaces as a route of extension. Excluding reports of isolated instances of perineural invasion, no exhaustive investigation of invasion of nerves had been undertaken until 1936 when Warren, Harris and Graves³² were struck with the frequency of its occurrence in prostatic carcinoma. Kahler,¹⁶ in a later study, placed perineural invasion at the head of the list of criteria for the microscopic diagnosis of prostatic carcinoma.

As early as 1770, Cotugno⁷ described spaces about the sciatic nerve which he demonstrated in the cadaver. Other investigators followed with studies to determine the anatomic nature of these spaces and the presence or absence of a definite communication with the spinal subarachnoid space. Key and Retzius,¹⁷ Orr and Rows,²⁵⁻²⁸ Weed,³³⁻³⁶ Alford and Schwab,¹ and Sullivan and Mortensen³¹ have contributed greatly through injection experiments on man and animals, to the knowledge of the nature of the neural spaces and of the direction of flow of the fluid therein.

The fact that these spaces exist about the nerves to their smallest ramifications, and that there is a circulating fluid medium within, gives rise to the contemplation of another possible mode of spread of neoplastic cells, and thus suggests a possible relation between recurrence and metastatic spread of a malignant growth and perineural invasion. This feature has been noted in rectal carcinoma but there has been little or no mention made in published reports of its possible relation to the recurrence and visceral spread of rectal carcinoma.

This study concerns itself with the incidence of perineural invasion in a series of cases, along with that of venous invasion and nodal spread, and an attempt to correlate their presence with available clinical data.

METHODS AND MATERIALS

One hundred gross operative specimens of rectal carcinoma removed by the abdominoperineal or the abdominal route at the Mayo Clinic, during the year 1935 and the early part of 1936, were chosen for study in the order of their removal. Specimens removed during these particular years were chosen so that a sufficient interval for adequate follow-up study of the patients who had the growths might have elapsed.

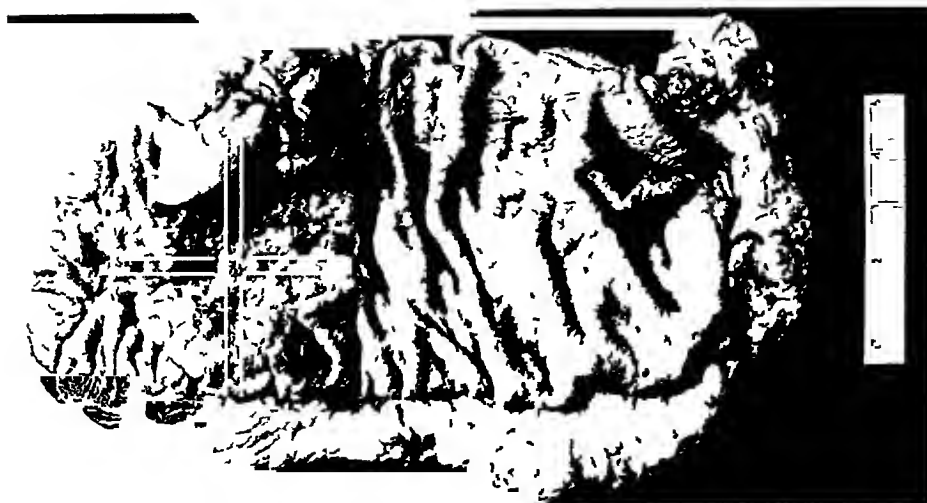


FIG 1—Surface view of lesion after bowel had been opened, showing location of blocks removed from each of four quadrants

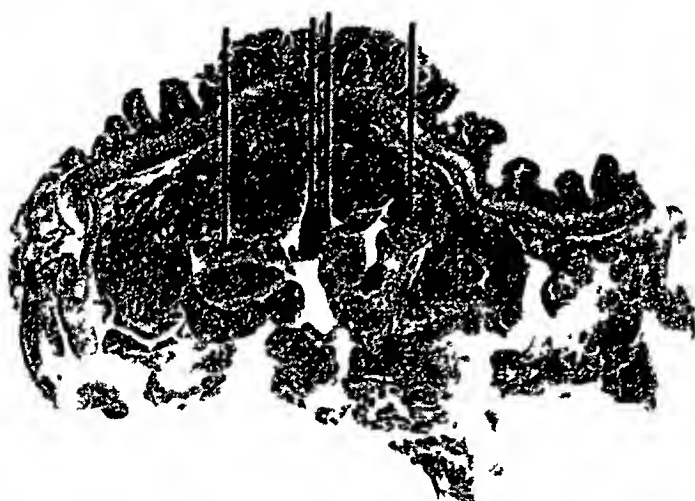


FIG 2—Cross section showing depth of blocks from the four quadrants. Normal mucosa and perirectal tissue included in each block



FIG 3—Posterior view showing cross cuts and location of blocks removed in search of venous and perineural invasion. Blocks extend through the perirectal tissue to the intestinal wall

To study the involvement of veins, blocks of tissue from all points of the lesion and rectal wall at which microscopic evidence of venous invasion could conceivably be present were removed. The lesion was divided into four quadrants and a block of tissue was taken from each quadrant. The block included the full-thickness of the lesion and the entire thickness of the rectal wall as well as a certain amount of perirectal tissue (Figs 1 and 2). In addition, transverse cuts were made through the perirectal fatty tissue, exposing the larger vessels leading from the vicinity of the lesion (Fig 3), and blocks were removed for microscopic study from regions which appeared suspicious, usually within a distance of four inches (10 cm) above and below the growth.

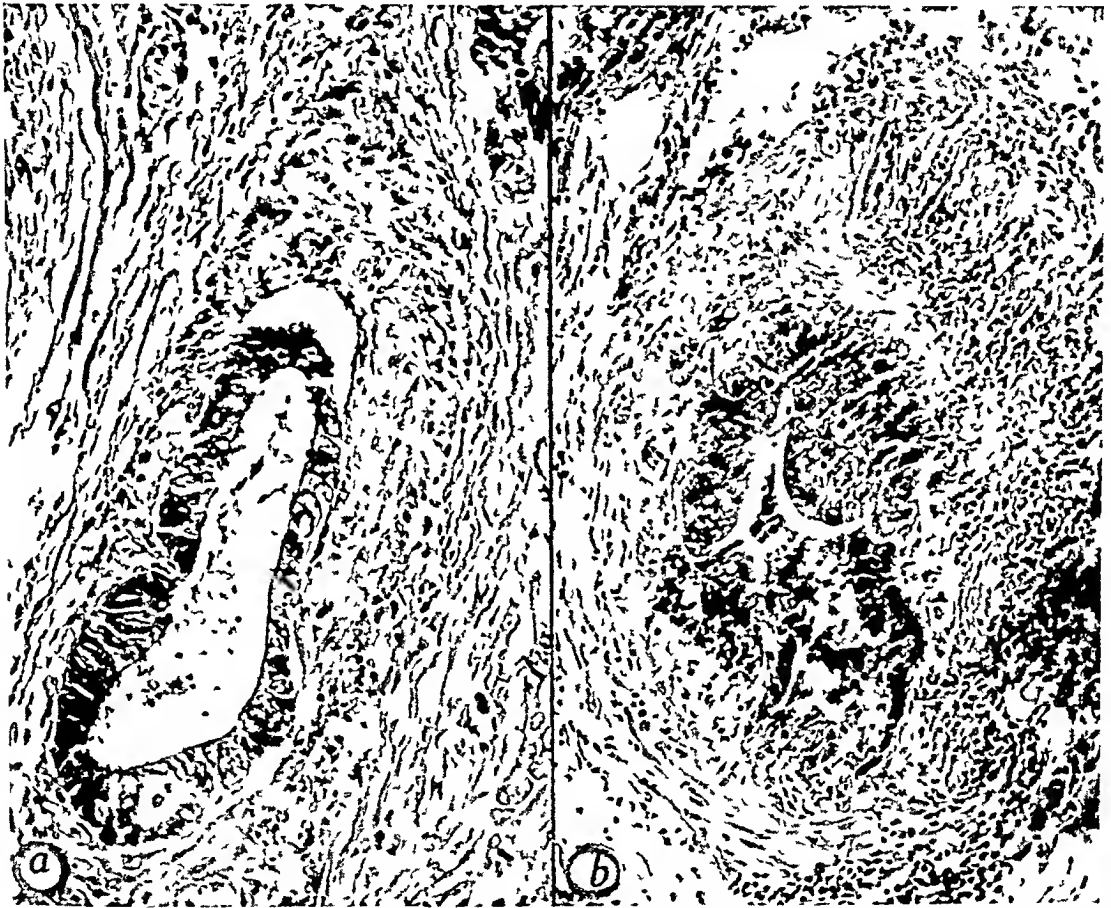


FIG 4—(a) Photomicrograph of small vein in the perirectal tissue, the lumen is lined by malignant cells ($\times 185$), (b) adenocarcinoma, Grade 4 (Broders' method), in the lumen of a small vein in the perirectal tissue ($\times 140$)

Preliminary microscopic examination of sections cut from the blocks, fast freezing technic being used, was facilitated by the use of an acid polychrome methylene blue stain, which is especially adaptable for tissues that have been long fixed in formalin. Of those tissues in which definite or presumptive evidence of venous or perineural invasion was found, permanent sections stained with hematoxylin and eosin were made and further study was carried out. We wish to thank Dr MacCarty, in whose laboratory the study was made, and Dr Dockerty, who reviewed the sections.

After examination of all sections was completed, results were tabulated and correlation with clinical data and follow-up records was attempted.

In this method of study, as in others reported to date, there were a few cases in which it was extremely difficult to distinguish small sub-mucosal lymphatic channels from venous channels, and in these cases van Gieson's stain was employed with some degree of success. The presence of erythrocytes within the lumen of a vessel may often aid in distinguishing the type of vessel, but it must be borne in mind that hyaline and necrotic

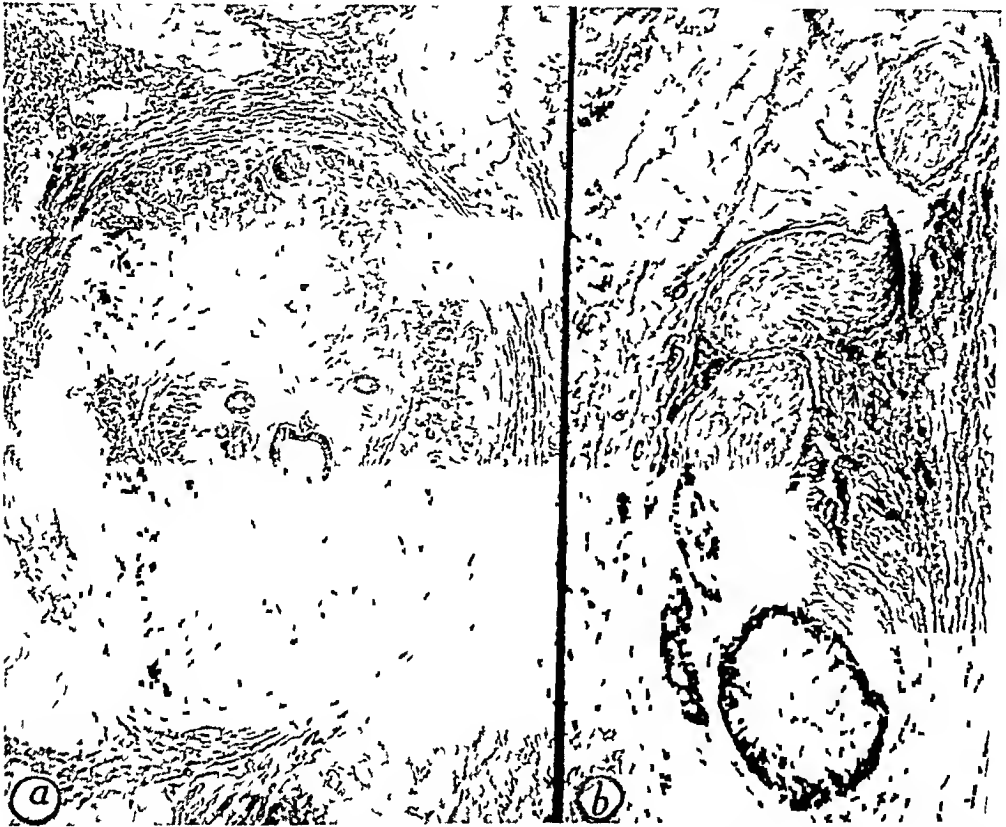


FIG 5—(a) Photomicrograph showing malignant canalization of a thrombus in a large vein in the perirectal tissue ($\times 35$), (b) invasion of perineural spaces by colloid adenocarcinoma, Grade 2, showing formation of alveoli and secretion of mucus. Note uninvolved nerve nearby ($\times 60$)

material may closely resemble erythrocytes, and also that lymphatic channels may contain erythrocytes as a result of trauma or the surgeon's knife. The presence of smooth muscle, as demonstrated by van Gieson's stain, is of some help.

Most of the involved veins were found in the perirectal tissue near to the muscle wall or within the perirectal fat (Figs 4 *a* and *b* and 5 *a*). There were no instances of invasion of an arterial lumen, a fact that emphasizes the oft-mentioned immunity of these vessels to carcinomatous invasion. Perivascular lymphatic vessels were seen to be involved, but there was no penetration of the arterial wall.

An interesting feature noted was the frequency of arterial thrombosis in cases in which the veins were involved. This occurred in a number of

instances, and when seen on preliminary examination was taken as an indicator of venous involvement

In arriving at the final microscopic diagnosis, we considered only cases in which the involved vessels were definitely venous and eliminated all cases in which the observations were indefinite

Perineural invasion is not as difficult to recognize as is involvement of venous channels. In most instances, involved nerves are abundant in the section, although by no means all of the nerves in one section are always involved. Many fields were examined in which a nerve was seen to be extensively involved whereas one or several nerves in the immediate vicinity were not involved (Fig 5 *b*). Invasion of nerves was seen as far as four inches (10 cm) from the site of the primary growth

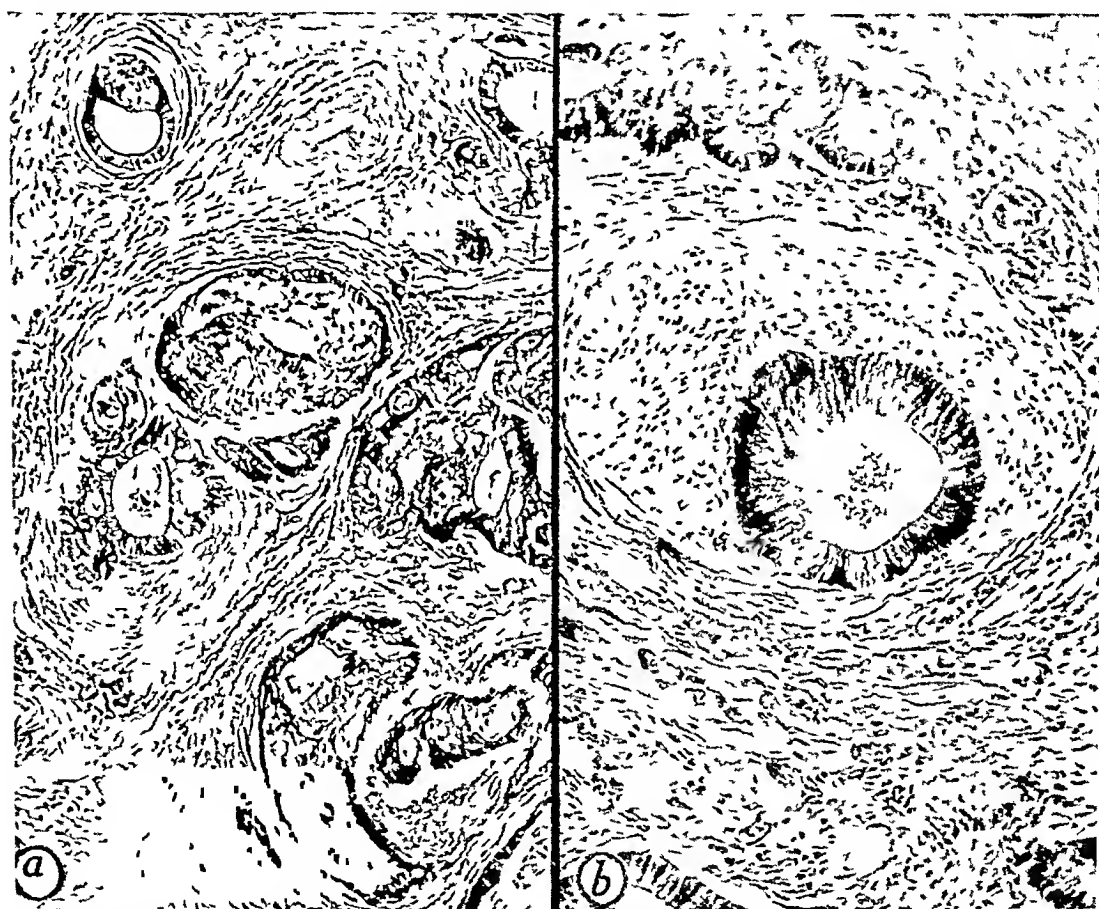


FIG 6 —(a), Photomicrograph showing extensive invasion of nerves with marked distention of the neural spaces, and formation of alveoli ($\times 70$), (b) showing alveolus in the endoneurial space with compression of the surrounding nerve fiber, but without degeneration of the nerve ($\times 125$)

Many cases were rejected because of “secondary” involvement of nerves. This was usually present in nerves close to the lesion. The nerve was completely surrounded by extensive carcinomatous infiltration but the perineural space remained intact and did not contain carcinoma cells within its confines, indicating that the nerve was merely isolated by surrounding carcinoma and not actually invaded.

Involvement of the perineural space varied in architecture. In some instances a few malignant cells were seen lying within the space without

any apparent conformation, while in other cases the cells were arranged in alveoli and even distended the space with their mucous secretion (Fig 6 a)

There was little or no degeneration of nerve fibers to be seen in the nerves involved, apparently because of the distensibility of the walls of the perineural spaces, which were seen to be extremely distorted in places (Fig 6 b)

In no cases were the plexuses of Meissner and Auerbach seen to be involved, although nerve fibers both proximal and distal to these structures might be invaded

RESULTS

Lymphatic Involvement—Involvement of the lymph nodes was found to be present in 47 per cent of the 100 cases. In previous investigations based, in total, on more than 500 specimens, the proportion of cases in which lymph nodes were involved varied from 36 to 68 per cent (Table I). We found,

TABLE I
NODAL INVOLVEMENT FOUND IN PREVIOUS STUDIES

Author	Total No of Cases	Percentage Involved
McVay	100	47
Wood and Wilkie ¹⁷	100	51
Gabriel, Dukes and Bussey	100	62
Gilchrist and David	25	68
Coller, Kay and MacIntyre	53	64
Grinnell (1916-1932)	107	36
Grinnell (1938-1941)	75	55

as others before us, that the higher the grade of malignancy (Broders' method) the higher the incidence of nodal involvement (Table II)

TABLE II

INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVASION ACCORDING TO GRADE OF MALIGNANCY (BRODERS)

Grade	Total Cases	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
1	14	3	21.4	2	14.3	1	7.1
2	54	20	37.0	16	29.6	7	13.0
3	24	18	75.0	9	37.5	7	29.2
4	8	6	75.0	3	37.5	5	62.5
Totals	100	47		30		20	

Dukes¹⁰ expressed the opinion that metastatic growths in lymph nodes are more frequently found among women than among men, a feature which is not borne out in this study, 46.1 per cent of women and 47.5 per cent of men having nodal involvement.

Dukes has stated that the highest incidence of nodal involvement occurs among young patients, while the tendency is less frequent among the older patients. This fact was also noted in this series (Table III).

Most investigators, notably Mayo and Schlicke,¹⁸ have found the highest

incidence of nodal invasion in the upper part of the rectum and in the recto-sigmoid. In this series a slightly higher proportion of nodal involvement was found in the middle third of the rectum than in the other segments, 50 per cent in the middle third, and 48.8 and 40.2 per cent in the upper and lower thirds, respectively.

Of the series of patients who had nodal metastatic lesions, ten patients survived for three years while only two survived for five years.

Perineural Invasion—Involvement of the perineural and endoneural spaces was demonstrated in 30 of the 100 cases, the average age of the patients who had perineural involvement being 51 years, almost exactly the average age in the entire series. Eighteen of the 30 patients were men (60 per cent), and 12 were women (40 per cent).

The average preoperative duration of symptoms among those patients who had involvement of nerves was 9.4 months, as compared with 9.7 months in the entire series. Pain was a prominent symptom, volunteered by the patient, in 24 cases, it was not mentioned in the history of three cases, and was stated

TABLE III
INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVOLVEMENT ACCORDING TO AGE

Age Years	Total Series	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
20-39	11	7	63.6	3	27.3	4	36.4
40-59	68	34	50.0	21	30.9	13	19.1
60-79	21	6	28.6	6	28.5	3	14.3
Totals	100	47		30		20	

to be absent in three cases. Thus, in 89 per cent of the cases in which information on this point was available, pain was a prominent symptom. In the evaluation of pain in this study, only cases in which the history indicated that the pain might be directly neurogenic and not just discomfort vaguely noted by most patients with rectal carcinoma, were recorded. Terms such as "aching," "boiling," "gnawing," "constant" or "steady" were considered to be indicative of pain due to involvement of nerves, while tenesmus, cramps, a feeling of fullness and the desire to defecate were not so considered. Of the 70 cases in which the nerves were not involved pain was found to be a primary symptom in only 25. Pain was not mentioned in the history of 20 cases, and in 25 cases, when the patient was questioned, he stated that it was definitely absent or was present in one form or another but not localized to the rectum. The incidence, then, of pain for cases without perineural involvement in which information was available was 50 per cent.

Of the 30 cases in which there was involvement of the nerves, the lymph nodes were also involved in 20 (67 per cent).

When involvement of nerves was considered in the light of grading, both by cellular differentiation (Broders) and by mural penetration (Dukes), it was seen that the higher the degree of malignancy, the more frequently was perineural involvement present (Tables II and IV).

any apparent conformation, while in other cases the cells were arranged in alveoli and even distended the space with their mucous secretion (Fig 6 a)

There was little or no degeneration of nerve fibers to be seen in the nerves involved, apparently because of the distensibility of the walls of the perineural spaces, which were seen to be extremely distorted in places (Fig 6 b)

In no cases were the plexuses of Meissner and Auerbach seen to be involved, although nerve fibers both proximal and distal to these structures might be invaded

RESULTS

Lymphatic Involvement—Involvement of the lymph nodes was found to be present in 47 per cent of the 100 cases. In previous investigations based, in total, on more than 500 specimens, the proportion of cases in which lymph nodes were involved varied from 36 to 68 per cent (Table I). We found,

TABLE I
NODAL INVOLVEMENT FOUND IN PREVIOUS STUDIES

Author	Total No of Cases	Percentage Involved
McVay	100	47
Wood and Wilkie ³⁷	100	51
Gabriel, Dukes and Bussey	100	62
Gilchrist and David	25	68
Coller, Kay and MacIntyre	53	64
Grinnell (1916-1932)	107	36
Grinnell (1938-1941)	75	55

as others before us, that the higher the grade of malignancy (Broders' method) the higher the incidence of nodal involvement (Table II).

TABLE II
INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVASION ACCORDING TO GRADE OF MALIGNANCY (BRODERS)

Grade	Total Cases	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
1	14	3	21.4	2	14.3	1	7.1
2	54	20	37.0	16	29.6	7	13.0
3	24	18	75.0	9	37.5	7	29.2
4	8	6	75.0	3	37.5	5	62.5
Totals	100	47		30		20	

Dukes¹⁰ expressed the opinion that metastatic growths in lymph nodes are more frequently found among women than among men, a feature which is not borne out in this study, 46.1 per cent of women and 47.5 per cent of men having nodal involvement.

Dukes has stated that the highest incidence of nodal involvement occurs among young patients, while the tendency is less frequent among the older patients. This fact was also noted in this series (Table III).

Most investigators, notably Mayo and Schlicke,¹⁸ have found the highest

incidence of nodal invasion in the upper part of the rectum and in the recto-sigmoid. In this series a slightly higher proportion of nodal involvement was found in the middle third of the rectum than in the other segments, 50 per cent in the middle third, and 48.8 and 40.2 per cent in the upper and lower thirds, respectively.

Of the series of patients who had nodal metastatic lesions, ten patients survived for three years while only two survived for five years.

Perineural Invasion—Involvement of the perineural and endoneural spaces was demonstrated in 30 of the 100 cases, the average age of the patients who had perineural involvement being 51 years, almost exactly the average age in the entire series. Eighteen of the 30 patients were men (60 per cent), and 12 were women (40 per cent).

The average preoperative duration of symptoms among those patients who had involvement of nerves was 9.4 months, as compared with 9.7 months in the entire series. Pain was a prominent symptom, volunteered by the patient, in 24 cases, it was not mentioned in the history of three cases, and was stated

TABLE III
INCIDENCE OF NODAL, PERINEURAL AND VENOUS INVOLVEMENT ACCORDING TO AGE

Age Years	Total Series	Nodal Involvement		Perineural Involvement		Venous Involvement	
		Cases	Percentage	Cases	Percentage	Cases	Percentage
20-39	11	7	63.6	3	27.3	4	36.4
40-59	68	34	50.0	21	30.9	13	19.1
60-79	21	6	28.6	6	28.5	3	14.3
Totals	100	47		30		20	

to be absent in three cases. Thus, in 89 per cent of the cases in which information on this point was available, pain was a prominent symptom. In the evaluation of pain in this study, only cases in which the history indicated that the pain might be directly neurogenic and not just discomfort vaguely noted by most patients with rectal carcinoma, were recorded. Terms such as "aching," "boring," "gnawing," "constant" or "steady" were considered to be indicative of pain due to involvement of nerves, while tenesmus, cramps, a feeling of fullness and the desire to defecate were not so considered. Of the 70 cases in which the nerves were not involved pain was found to be a primary symptom in only 25. Pain was not mentioned in the history of 20 cases, and in 25 cases, when the patient was questioned, he stated that it was definitely absent or was present in one form or another but not localized to the rectum. The incidence, then, of pain for cases without perineural involvement in which information was available was 50 per cent.

Of the 30 cases in which there was involvement of the nerves, the lymph nodes were also involved in 20 (67 per cent).

When involvement of nerves was considered in the light of grading, both by cellular differentiation (Bioderis) and by mural penetration (Dukes), it was seen that the higher the degree of malignancy, the more frequently was perineural involvement present (Tables II and IV).

TABLE IV

Class	INCIDENCE OF PERINEURAL AND VENOUS INVASION ACCORDING TO DEGREE OF MURAL PENETRATION (DUKES)			
	Perineural Involvement		Venous Involvement	
	No of Cases	Percentage of Involved Cases	No of Cases	Percentage of Involved Cases
A	0		0	
B	10	33.3	3	15
C	20	66.7	17	85
Totals	30	100.0	20	100

There is no apparent relation between the size of the carcinoma and the presence of perineural invasion.

In considering the presence of perineural invasion in relation to the location of the growth, it seemed feasible to divide the rectum into lower, middle and upper thirds, including lesions of the rectosigmoid in the latter group. It was found that lesions exhibiting involvement of the nerves occurred equally in the three locations (ten cases in each third), so that the presence of perineural invasion is apparently not related to the location of the lesion. This result contrasts with involvement of lymph nodes, which, in this series, was more frequent in the middle and upper thirds of the rectum than in the lower third, and vascular invasion, which seems to increase with the height of the lesion in the rectum.

No relation could be observed between the location of the lesions (anterior, posterior or lateral wall) and the presence of involvement of nerves. Sixteen (53.3 per cent) of the lesions in which nerves were involved were annular in type and the rest were located at different points on the rectal wall. In the entire series, 30 lesions (43 per cent) were annular.

TABLE V

RELATION OF PERINEURAL INVASION TO LOCAL RECURRENCES

	Nerves Involved		Nerves Uninvolved	
	Cases	Percentage	Cases	Percentage
Definite local recurrence	13	81.2	14	30.4
Definitely no local recurrence	3	18.8	32	69.6
Totals	16	100.0	46	100.0
Questionable and inadequate follow-up and post-operative complications	14		24	
Grand Totals	30		70	

The striking feature of perineural involvement of rectal carcinoma is its relation to local recurrences (Table V). Only recurrences in the scar or site of anastomosis were considered. Metastasis to nearby viscera, such as the bladder, vagina, prostate, perineal nodes, etc., was eliminated because of the probability of its being due to lymphatic or venous spread rather than to invasion of nerves. Definite local recurrences were found in 81.2 per cent of traceable cases in which there was perineural invasion, whereas, in those without perineural invasion, recurrences occurred in only 30.4 per cent. Cases in which there were definitely no local recurrences comprised only 18.8 per cent of those in which nerves were involved, whereas, in cases

without involvement of nerves there were definitely no recurrences in 69.6 per cent. It was necessary to eliminate certain cases from each group in comparing these results. These were considered to have been followed-up inadequately because of early deaths from unrelated causes, such as post-operative peritonitis or pulmonary embolism, and unconfirmed causes of death. All cases in which there was a question as to local recurrence, but no reliable evidence was found to substantiate its presence, were placed in the latter group.

In the cases in which there was definite recurrence, there were nine (69.2 per cent) in which lymph nodes were involved in the group in which perineural invasion occurred, and there were seven (50 per cent) in which lymph nodes were involved in the group without perineural invasion. While these figures tend to indicate a somewhat greater degree of lymphatic spread in those cases of recurrence in which nerves are involved, they are not statistically significant, and, in any case, do not necessarily prove that recurrence is dependent on the lymphatic system rather than on the nerves. Nodal involvement in the entire series, in cases in which there was perineural involvement, was 66 per cent. Nodal involvement was 64.7 per cent (11 cases in 17) in those cases in which there was invasion of the nerves but no local recurrence.

There was a notable difference in the five-year survival rates of the patients who had, and those who did not have, perineural involvement. In the group of 29 traced cases in which there was perineural involvement, only two patients were living and well five years after the operation (6.9 per cent). Twenty-three were dead from cancer, either recurrent or metastatic, and of these, 19 were dead within two and one-half years. The average duration of life after operation of the 23 who died within five years, eliminating four patients who died because of postoperative complications, was 20 months.

In the group in which involvement of nerves was not found at operation, it was discovered that 18 of 51 patients who were traced, were living after five years (35.3 per cent). The average duration of life after operation in this group, of those who did not survive for five years was 25.7 months.

In the group in which there was perineural involvement, four patients, sooner or later, complained of a great deal of severe sciatic pain, which might be taken as a possible indication of further spread to greater distances, of the malignant cells within the perineural spaces. All four of these patients died within 15 months after operation of visceral metastatic lesions.

It has been mentioned earlier that perineural invasion can be traced for a considerable distance in some cases. Although measurements of this entire distance were not carried out in this study, perineural invasion did occur as far as four inches (10 cm) from the site of the primary lesion. One might speculate that the invasion of the perineural spaces can take place to a distance above the line of operative resection and, at a later date, burst through the confines of the perineural space to give rise to a recurrent

lesion, perhaps at the line of anastomosis or at a higher level. Many sections showed a nerve surrounded by malignant cells. In these instances the perineural sheath appeared to be ruptured as though the cellular contents of the sheath had become too great for the distensibility of the membrane. In sections exhibiting 'secondary' nerve involvement, that is, isolation of a nerve by infiltrating carcinoma without penetration of the perineural membrane by the cells, the membrane was always intact, although completely surrounded by malignant cells.

Venous Invasion—In 100 cases of rectal carcinoma studied in this series there was evidence of invasion of the veins in 20 cases. There may have been venous involvement in two others, but confirmation of its presence was impossible by the methods used.

The average age of the patients who had venous invasion was 47 years. The average duration of symptoms in cases in which there was invasion of the veins was 7.9 months. The duration of symptoms in these cases varied from three weeks to 30 months.

There were 13 men (65 per cent), and seven women (35 per cent) among the patients who had venous invasion.

The incidence of venous invasion in relation to histologic grading, according to cellular differentiation and to mural penetration (Tables II and IV) increased with the degree of malignancy. Only three of the 20 cases in which there was venous invasion fell into Dukes' Class B, while 17 cases fell into Class C. There were no cases in Class A.

Nodal involvement was present in all except three of the cases in which there was venous invasion (85 per cent). This would indicate that venous invasion rarely occurs before nodal involvement, but that it may do so.

In relating the frequency of venous invasion to the location of the lesion, we found that in lesions of the upper part of the rectum and rectosigmoid invasion was present more often than in lesions of the lower segments, the upper third in 55 per cent, and the middle and lower thirds in 15 and 30 per cent, respectively.

The postoperative survival of patients who had venous invasion was found to vary from four to 60 months, the average survival being 22 months. Three patients survived for three years, one patient for four years, and one for five years. The latter died exactly five years after operation, and, at necropsy, lesions were observed in the liver. Sixteen of the 20 patients finally succumbed to cancer.

In eight of these 20 cases venous invasion alone was observed, while in 12, perineural involvement was observed in addition to venous invasion. In 16 cases in the general series, involvement of nerves without venous invasion was observed.

In the total series of 100 cases, there were 27 local recurrences. In six of these, nerve invasion alone was observed (22.2 per cent), in three, venous involvement alone (11.1 per cent), in seven, involvement of nerves and veins together (25.9 per cent), and in 11, involvement of neither nerves

METASTASES OF CANCER OF RECTUM

nor veins (40·7 per cent) In only four of the cases without involvement of nerves or veins was involvement of nodes observed Therefore, in seven cases there was recurrence in spite of the fact that involvement of any of the three pathways of spread was not observed at operation

Recurrence of rectal carcinoma, in the light of these findings, is probably not concerned with only one of the three pathways of spread, but results from different ones in different cases, and may involve any of them However, it may be said that local recurrences are more frequent in rectal carcinoma when nerves and veins are involved than when they are uninvolved, and that there are twice as many recurrences when nerves alone are involved as when veins alone are involved

In studying the relation of the three pathways of spread of rectal carcinoma to the presence of visceral metastatic lesions occurring at operation and later, it was found that metastatic lesions were present or occurred later most frequently in the group that showed venous invasion (Table VI)

TABLE VI

OCCURRENCE OF VISCERAL METASTATIC LESIONS AT OPERATION, AND LATER IN CASES IN WHICH THERE WAS NODAL, PERINEURAL OR VENOUS INVASION

	Entire Series		Nodal Involvement		Nerve Involvement		Vein Involvement	
	Cases	Percentage	Cases	Percentage	Cases	Percentage	Cases	Percentage
Metastatic lesions present at operation, or occurring later	31	45·6	22	78·6	13	81·2	16	94·1
Metastatic lesions	37	54·4	6	21·4	3	18·8	1	5·9
Totals	68	100·0	28	100·0	16	100·0	17	100·0
Inadequate follow-up and postoperative complications	32		19		14		3	
Grand totals	100		47		30		20	

In 94 per cent of the cases in which venous invasion was observed at operation and in which the follow-up was adequate, visceral metastatic lesions either were present at the time of operation or developed later, whereas, visceral metastatic lesions were less frequent in cases in which nerves or nodes were invaded This fact would seem to indicate that venous invasion is important in regard to visceral metastasis while perineural invasion may be related to local recurrence

In the entire series of 100 cases, visceral metastatic lesions were found at the time of operation in seven cases, and in six of these, venous invasion was present in the specimen removed (86 per cent) Lymph nodes were involved in five of these seven cases (71 per cent)

In only four of the 20 cases in which there was venous invasion were metastatic lesions observed in the liver at operation, and the surgeon made the diagnosis of malignancy by palpation correctly in three instances

When one considers that one-fifth of the patients in this series of rectal

carcinoma had veins invaded by carcinoma, and that practically all (94 per cent) of these already presented, or later acquired, visceral metastatic lesions, the prognostic importance of the presence of venous invasion in the operative specimen is seen. The fact that four-fifths of the patients in the series of 100 cases failed to show invasion of the veins at operation and that visceral metastatic lesions occurred in only 18.7 per cent (15) of these patients emphasizes the prognostic significance of the absence of venous invasion, as has been mentioned by Brown and Warren³

CONCLUSIONS

1 In 100 cases of rectal carcinoma, lymph nodes were involved in 47 per cent, nerves in 30 per cent, and veins in 20 per cent

2 Invasion of lymph nodes, nerves and veins increases with the degree of malignancy of the carcinoma

3 Invasion of lymph nodes occurred equally in the two sexes, while venous invasion and perineural invasion were more frequent among men than among women

4 Venous and nodal invasion occurred more often among young than among old patients, while invasion of nerves was not related to age

5 Invasion of nerves was not related to the location of the lesion, while venous invasion was most frequent in lesions of the upper part of the rectum, and nodal invasion was slightly more frequent in lesions of the middle segment of the rectum than in lesions of other segments

6 Venous invasion occurred more frequently in cases in which there was involvement of nodes than in other cases, but it occurred in cases without involvement of nodes as well

7 Nodal invasion was somewhat more frequent in cases in which there was involvement of nerves than in those in which the nerves were not involved

8 Pain was a prominent symptom in 89 per cent of cases in which there was invasion of nerves

9 Local recurrence was more than two and one-half times as frequent in cases in which invasion of nerves was observed as in cases in which it was not observed

10 Visceral metastatic lesions at operation, or later, occurred in 94 per cent of patients who had venous invasion in the primary growth, and were five times as frequent as in patients without venous invasion in the primary growth

11 Venous invasion in the primary growth does not always mean that hepatic metastatic lesions are present

12 Eighty-six per cent of patients among whom visceral metastatic lesions were present at operation exhibited venous invasion in the primary growth, while 71 per cent exhibited nodal invasion

13 Eighty per cent of patients who had venous invasion in the primary growth died from carcinoma, either recurrent or metastatic

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CHOLEDOCHUS CYST¹

FINAL REPORT OF TWO CASES

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FROM THE SURGICAL SERVICES OF THE GERMANTOWN DISPENSARY AND HOSPITAL, AND CHESTNUT HILL HOSPITAL, PHILADELPHIA, PA

Case Report—K E, age 22, white, female, married, was admitted to the medical ward of the Chestnut Hill Hospital, September 9, 1940, and discharged September 18, 1940. She was readmitted for the same condition as a private patient of Dr William C Sheehan, now Lieutenant Colonel Sheehan, U S A, October 7, 1940, and discharged October 25, 1940. She was again readmitted to the service of Doctor Sheehan, October 16, 1941, and died October 22, 1941, of general peritonitis following rupture of a liver abscess.

Chief Complaint—Pain and a tumor in the right upper abdomen and jaundice.

History of Present Illness—Patient's symptoms were first noticed before her baby was born August 19, 1940. During the fourth and fifth months of her pregnancy there occurred occasional pains in the right upper quadrant of her abdomen. She described these pains as stomach pains since they were exaggerated when she ate. They were so severe and colicky in character that she was brought into the maternity ward and was given urinary antiseptics. Several months after the stomach pain, the pain shifted to the back and well up toward the shoulder, where it became constant, at first excruciating and then gradually decreasing in intensity until after one and one-half months, when the pain left her entirely, but the seventh month of her pregnancy she noticed a slight yellowish tinting of the skin, which came and went at irregular intervals and never became a real deep yellow. There also was an irregular diarrhea that continued almost until full term. Two weeks before the birth of the baby the mother looked very well, and there was no jaundice until 12 days after the baby was born. Then suddenly jaundice set in and increased in severity and remained constant. At this time a mass was noticeable in the right upper quadrant of the abdomen about the size of a grapefruit. This mass was noticed during the seventh and eighth months of pregnancy but had not been diagnosed as abnormal in any way, being taken for the fetus. There was no pain in this area for the last two months. **Past Medical History**—Measles, catarrhal jaundice at age of 12. Influenza at five years of age. **Social History**—Married, one child. **Family History**—Irrelevant.

Physical Examination—The patient was a white female, age 22, jaundiced. Frail build but muscular tone good. The positive findings were as follows. Skin Jaundiced. No petechiae. Abdomen Liver enlarged, palpable at least five fingers breadth below the costal margin. Gallbladder questionably enlarged, though apparently it seems as though there is a hydrops. Mass can be pushed downward with the palm of the hand obliterating everything except the liver edge. No herniae. **Laboratory Data** Icteric index increased, van den Bergh 3.0 mg % bilirubin, urine loaded with white cells. **Clinical Impression** Hepatitis, hydrops of gallbladder.

Progress Notes—One thousand cubic centimeters of 5% glucose in normal salt solution were given on September 10, 11, 12, 13, 15 and 16. September 18, 1940, discharged, and allowed to go home. If jaundice does not lessen in severity she is to be readmitted to the Surgical Service. Our Surgical Service was asked to see this patient in consultation during this admission but since the patient showed signs of lessened jaundice and decrease in the size of the mass she was allowed to go home.

* Read before the Philadelphia Academy of Surgery, December 7, 1942

Second Admission—Surgical Service of Dr Sheehan Admitted October 7, 1940 Discharged October 25, 1940 Patient was readmitted 19 days after discharge from the hospital, with persistent jaundice, and a tumor in the upper right quadrant equally as large as on previous admission, and the liver enlarged four fingers' breadth below the costal margin After several days preoperative preparation the patient was scheduled for operation with the possible diagnosis of hydrops of the gallbladder

Operation—October 11, 1940 by Doctor Sheehan Under nitrous oxide and oxygen anesthesia, the abdomen was opened A large cystic mass was found under the right lobe of the liver with a gallbladder with its cystic duct resting on it and emptying into the cystic mass A needle was inserted into the mass and bile-colored fluid obtained A cholecystectomy and choledochoduodenostomy and appendicectomy were performed About 1560 cc of bile were removed from the cyst Intravenous glucose 5% in 2000 cc salt solution was given

The patient was discharged October 25, 1940, after a rather stormy convalescence The jaundice had gradually faded

Third Admission to Chestnut Hill Hospital—Admitted October 16, 1941, and died October 22, 1941 *History of Present Illness*—Patient was in her usual health having recovered from a choledochoduodenostomy on October 10, 1940, until October 12, 1941, when she experienced five or six chills, after which her temperature rose to 101° F She had severe, drenching night sweats which required changing the bed every two hours Loss of four or five pounds in the past three months Usual weight 98 pounds No cough Had slight nausea with no vomiting Appetite was good before onset of present symptoms

Progress Notes—October 18, 1941 Temperature 101° F Feels flushed W B C 18,650 as compared with count on admission of 11,400 R B C 3,000,000 Hemoglobin 61% October 19, 1941 Chills and fever this P M Temperature 102.6° F Pain in left upper abdomen radiating to lower abdomen Also complains of chest pain Abdomen somewhat distended Chills frequent, spleen seems enlarged to percussion but is not palpable Given intravenous glucose 5%, 1000 cc October 20, 1941 W B C 9,000, Polys 78% Given glucose 5% and salt, 1000 cc Temperature, pulse and respirations fell to subnormal level this P M General condition worse October 21, 1941 Given 500 cc citrated blood Barium enema today shows no evidence of a large bowel pathology, evidence of small intestinal obstruction Blood chemistry Chlorides 468, protein 67, CO₂ 47, blood urea nitrogen 20 Temperature elevated this A M, down this P M Pulse rate stays elevated Distention much increased Peristalsis not heard Advised operation Condition not good

Operation—October 22, 1941 Exploration revealed a massive pus collection in the abdomen and general peritonitis Over three pints of creamy pus were aspirated Appendix not located Choledochal cyst found to be much decreased in size Sulfanilamide powder was sprinkled into the abdominal cavity and several drains were inserted Postoperative condition poor Given fluids and blood transfusion and put in an oxygen tent, but condition became worse, and she expired shortly after operation was completed

Autopsy Report (Three hours after death) *Peritoneum and Gastro-intestinal Tract* The entire peritoneum is involved in a diffuse and localizing inflammatory reaction Every surface is covered by white fibrinous exudate which forms easily broken adhesions between the omentum, loops of bowel, body wall and all the intra-abdominal structures In many locations these adhesions enclose similar or larger collections of thick creamy pus Such collections are found everywhere but are more common in the upper parts of the abdomen There are large deposits between the liver and the diaphragm One such collection between the left lobe of the liver communicates with an irregular, ragged abscess cavity within the organ The stomach contains a small

CHOLEDOCHUS CYST

quantity of brownish fluid. Its structure is normal and its mucosa quite intact. The duodenum contains similar fluid and is equally normal. The ampulla of Vater projects from the surface and is easily identified. About 3 cm proximal to it there is a small ostium which admits a grooved director easily and leads into a cystic structure described below. The remainder of the small and large bowel shows no lesions nor any point of weakness to suggest the possibility of leakage. There is no trace of an appendix.

Liver Is normal in size, pale, rounded. The external surface is involved with the inflammatory process described. The viscus cuts easily. In the dependent portions of the left lobe there is a small, irregular, ragged abscess cavity described. This is about 6 cm square and extends no further into the liver than 3 cm. Beneath the right lobe and projecting so, from the liver substance, as almost to seem a separate structure, is a cyst, approximately 9 cm in diameter, with a thick, inflamed fibrous wall, into which liver tissue projects, filled with a thick greenish-yellow pus. Internally this is ragged and resembles an abscess.

Biliary Tract The gallbladder has been removed and the gallbladder fossa is filled with scar tissue. The nature of the ampulla of Vater has been described. Proceeding upward from this structure is a small normal common duct about 15 mm in length. From this point it dilated immediately into a cystic space, approximately 3 cm in diameter and about 10 cm in length, which extends into the sagittal fossa of the liver. One side of it is attached to the duodenum and through this region runs the ostium described above. The cyst is not regular in shape but has four or five arms that project for a centimeter or two into the surrounding tissues. Several of these penetrate the liver and connect with the bile ducts in that organ. The cyst is lined by a thin, smooth, pale membrane and is filled with flakes of brown crystalline material that resembles crust. The same material is found in the larger intrahepatic bile duct in the neighborhood.

Pancreas Is normal in size and shape. Its tissues are pale and show no abnormality. Wirsung's duct is easily patent for some distance above the ampulla of Vater.

Bacteriology Culture of liver abscess and peritoneum reveal 1. Streptococcus ignavus, nonhemolytic. 2. An unidentified enterobacterium probably belonging to the genus Proteus.

Pathologic Diagnosis Heart—Apparently normal. Lungs—Bronchopneumonia. Spleen—Passive congestion. Kidney—Toxic nephrosis. Urinary tract—Apparently normal. Genitalia—Apparently normal. Peritoneum and Gastro-intestinal tract—Acute peritonitis, acute perihepatitis. Biliary tract—Choledochal cyst with choledochoduodenostomy. Pancreas—Acute peripancreatitis. Adrenal glands—Lipoid diminution. *Cause of Death* Liver abscess with rupture and peritonitis.

COMMENT

A choledochus cyst (also reported as Congenital Cystic Dilatation of the Common Duct or Diverticulum of the Common Bile Duct) is interesting because of its pathology, diagnosis, treatment and complications or sequelae.

A true choledochal cyst represents a localized dilatation, primarily of the common duct, and the gallbladder is rarely enlarged.

The liver is frequently enlarged and cirrhotic. In a minority of cases the intrahepatic ducts are grossly dilated. Microscopically, there is often a cirrhosis with increased periportal connective tissue, proliferation of the bile capillaries, and rarely some bile stasis. Infection is common, and leukocytic infiltration of the portal areas may be marked. Cholangitis may reach an advanced stage, and intraductal suppuration has been seen.

DIAGNOSIS

It is a double satisfaction to diagnose these cases preoperatively and, again, at operation. Preoperatively, the diagnosis should be simple, since the outstanding three symptoms, namely, (1) pain in the right upper abdomen, (2) cystic tumor mass in the same area, and (3) jaundice, are the most likely to result as the lesion develops. However, the diagnosis is not often correctly stated. In a very complete article written by Zinninger and Cash,¹ in April, 1931, they state, "that the correct diagnosis before operation was apparently made three times in the 83 cases reported, and in many instances the true condition was not recognized at operation. Such errors will doubtless be repeated in the future, as few surgeons actually see a patient with this lesion. Therefore, unless the clinical picture is clear in the mind of the observer, it is unlikely that a correct preoperative diagnosis will be made."

TREATMENT

We have agreed that the treatment is choledochoduodenostomy. It is the simplest operation and the least shocking to the patient. Gross reports that in a group of 52 children originally collected and studied, the mortality was 69 per cent, but in those treated by primary anastomosis of the biliary tract and intestines, the mortality was nine per cent. Again, Ladd and Gross² definitely state that in many cases exploration has been continued unduly long, so that therapeutic procedures had to be curtailed because of onset of surgical shock. It is, therefore, pertinent to emphasize that, "the surgeon must be familiar with the pathology of this condition," for only then can he quickly recognize the lesion and rapidly promote drainage of the biliary system into the intestine, which has proved to be so efficacious in curing these individuals. Thus, even if the diagnosis is not made preoperatively, the probabilities of a cure are high if the condition is recognized at the operating table and proper treatment is immediately instituted.

In a number of cases the cyst has been drained externally in the hope of joining the ductal system and intestine at a later date. Such external drainage of the cyst has been followed by an exceedingly high mortality. Excision of the cyst should never be attempted. Doctor Weeder and the author originally thought in our case with a double duct and a cyst on the right one, that there was an advantage in excising it but we now agree that there is none. At the autopsy of Doctor Sheehan's case we found that the sac of the cyst had decidedly shrunk after a year's anastomosis (choledochoduodenostomy). This fact has many times been proven.

COMPLICATIONS OR SEQUELAE

In these two cases that I have seen and studied, the first case with Doctor Weeder,³ the patient developed a cirrhosis of the liver after excision of the cyst from the right common duct. The second case, seen with Doctor Sheehan, developed a liver abscess and general peritonitis. The latter patient was well for a year after the choledochoduodenostomy, cholecystectomy

and appendectomy, but then suddenly developed peritonitis, the result of a ruptured liver abscess, which resulted in her death

There is a general impression that life expectancy is rather short after an internal biliary fistula has been established. This is largely due to the fact that in dogs an ascending infection through the bile passages occurs and death follows rather early. We may seriously question the truth of this observation as applied to man, if one reviews the statistics.

In our first case, in which cirrhosis of the liver developed, the boy was operated upon December 13, 1932. The child remained entirely well until January 1, 1936, when he complained of some generalized pain and distention of the abdomen. Two masses were palpable, with enlargement of the abdominal veins and also ascites. The laboratory reports showed a decided anemia, and a diagnosis of splenic anemia was made. A splenectomy was performed February 5, 1936. The child did fairly well except for variations in his blood counts until September 23, 1937, when he complained of great fatigue, nausea and vomited a large amount of bright red blood. He vomited blood again September 25, 1937, and was readmitted to the hospital, he improved definitely under treatment and was discharged November 11, 1937. After his discharge he steadily improved. There was no evidence of gastro-intestinal or other bleeding and his blood count in February, 1938, showed red cells 3,950,000, hemoglobin 63 per cent, white blood cells 10,100, polymorphocytes 48%, lymphocytes 37%, monocytes 12%, eosinophils 2%, and basophils 1%.

At the Joint Meeting of the Philadelphia Academy of Surgery and the New York Surgical Society at Philadelphia February 9, 1938, Doctor Weeder⁴ reported the sequelae and complications of this case and, in conclusion, stated "certain questions are raised for which we have not the answer. It is interesting, however, to speculate upon them. Are these complications, the blood dyscrasia and the gastro-intestinal hemorrhage both the result of back pressure on the portal system, resulting from the atrophy of the right half of the liver and the fibrosis in the remaining part? Has the back pressure produced changes in the normal physiology of the spleen, resulting in alterations in function of the reticulo-endothelial system? If this be so, does Banti's disease originate in the liver, and is it the result of changes in that organ produced by toxins, either infectious, metabolic or disturbed endocrine secretions?"

In discussing Doctor Weeder's follow-up of this case, and in answer to the questions asked, Dr. Allen O. Whipple, of New York, gave a very interesting deduction and stated that "The subsequent history of this case, with the development of a splenomegaly in the presence of a cirrhosis with portal-bed obstruction has greatly interested me. We have been greatly interested in our Combined Spleen Clinic, at the Presbyterian Hospital, in the pathogenesis of splenomegaly. In some patients, undoubtedly, intra-hepatic portal obstruction results in a splenomegaly. In other cases, with thrombophlebitis of the splenic or portal vein proximal to the liver, spleno-

megaly developed without liver changes. In still others, portal-bed irritation, as seen in schistosomiasis and in dogs following silica powder injections of a portal radical, splenomegaly is associated with cirrhosis. In all of these several pathogeneses, the clinical picture is Banti's syndrome, *i e*, an anemia, a leukopenia, a low platelet count, and an enlarged spleen."

We are now interested to have the follow-up of all these cases that show a cirrhosis of the liver, in order to determine whether or not the cause is congenital or caused by interference at operation upon the choledochus cyst.

The child which Doctor Weeder and I operated upon December 13, 1932, was finally admitted to the Germantown Hospital, July 18, 1942, again suffering from gastro-intestinal hemorrhage from esophageal varices due to his portal obstruction, which finally resulted in his death July 23, 1942. At autopsy, a very pronounced cirrhosis of the liver was found with large esophageal varices. No other unusual ducts were found except the remaining common bile duct which was greatly contracted.

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ROUTINE CYSTIC DUCT DRAINAGE FOLLOWING CHOLECYSTECTOMY

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IT is not necessary to defend the statement that calculi are sometimes "left behind" in the common bile or hepatic bile ducts following operations upon the biliary tract. This is especially true when cholecystectomy only has been performed. However, the incidence is decreased if the biliary ductal system is thoroughly and systematically explored, and it varies in direct ratio to the experience of the operator and the methods used for exploration. Nevertheless, this unfortunate happening is always a possibility, and in some cases a probability. Because a remaining calculus in this location is ever a potentially serious, and even a fatal, complication, its consequences are worthy of prevention when and where possible. On the other hand, it is just as important to know that ductal calculi are absent as it is to know that they are present, particularly if a patient has symptoms following cholecystectomy. Hence a brief discussion of a simple, safe and very satisfactory method of determining these facts in every operative patient before they leave the hospital. The advantages of such knowledge are obvious.

The ideal procedure is a roentgenologic study of the common bile duct made on the operating table, using contrast media—but this is rarely done (the immediate cholangiogram). This procedure will undoubtedly be in more common use in the near future. It has, of course, certain disadvantages, but these are outweighed by its advantages. It not only decreases trauma and the operating time in the doubtful case by showing the absence of calculi, and that the duct need not, therefore, be opened, but if stones are present it shows accurately their number, size and position. Thus the immediate cholangiogram greatly reduces the incidence of secondary operations, with their higher morbidity and mortality rates. However, in those hospitals which have not the facilities for immediate cholangiography, such studies can be made at a later date on every patient—preferably before they leave the hospital—through a cystic duct drain introduced at the time of cholecystectomy. (Cholangiography is *always* a *must* procedure in all patients who have a mushroom catheter in the gallbladder or a tube in the common duct.)

A small rubber catheter is placed in the remaining (proximal) cystic duct and securely tied with 40-day chromic catgut. If the diameter of the duct is small it may occasionally be necessary to cut the duct longitudinally before the catheter can be inserted, which was necessary in the case herein presented. The introduction of the tube takes only a few minutes longer than clamping and tying the cystic duct stump because this entire area must be clearly

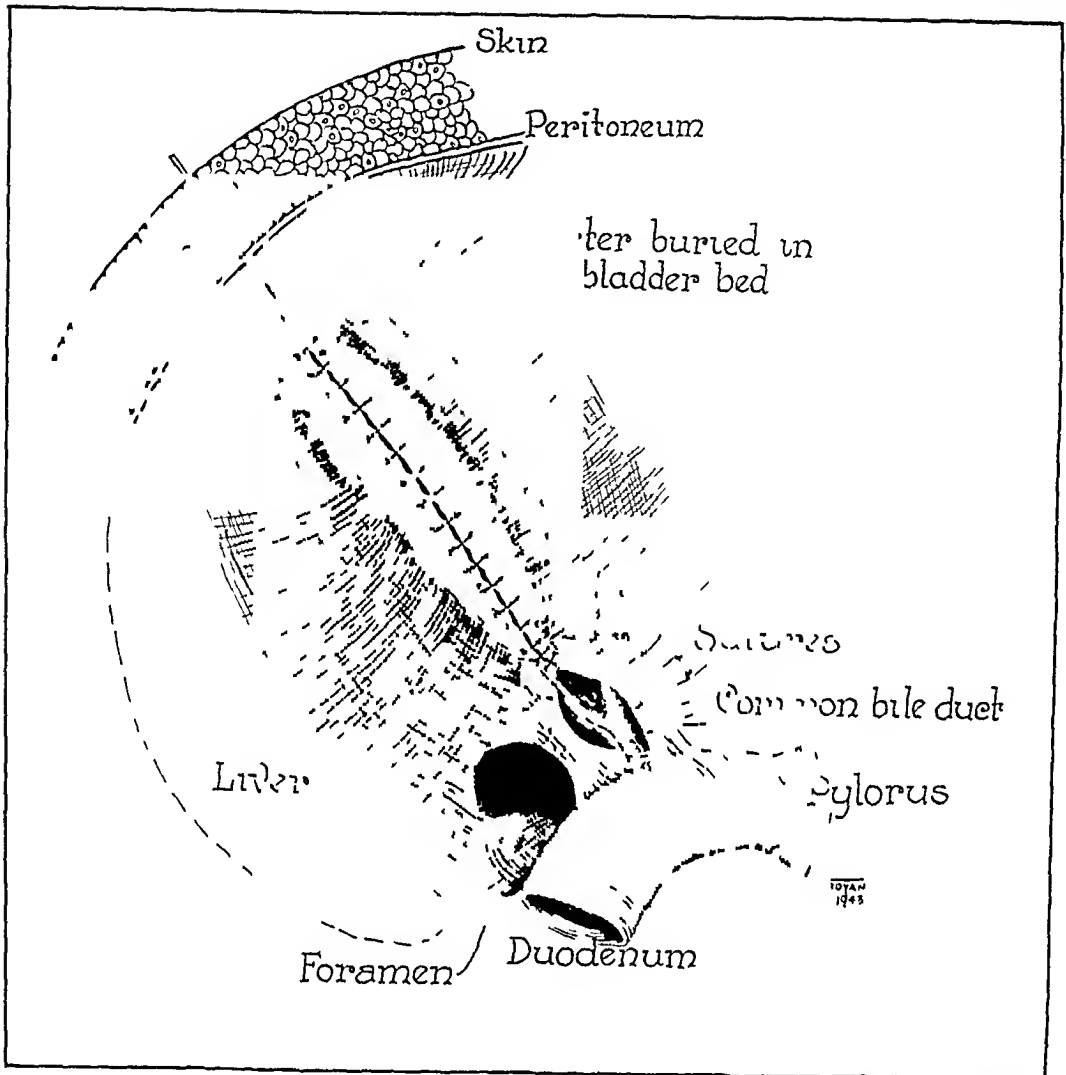


FIG 1—A semidiagrammatic drawing to illustrate the position of the catheter in the reperi-tonealized liver bed. The sutures will close the opening over the ductal juncture. Omental grafts should cover any defects in such a way that no bare areas remain.

visualized before the gallbladder is removed, whether or not the catheter is used. The catheter is then brought to the abdominal wall in the reperi-tonealized bladder bed (*i.e.*, under the peritoneum) and makes exit from the abdominal wall through a small stab wound immediately above the point where the catheter leaves the liver edge (Fig 1). It may rarely be necessary to cover any bare areas with an omental graft, or a sleeve of omentum may have to be used to cover any length of rubber which is not retroperitoneal. In this way the foreign body is completely retroperitoneal except for a short distance between the liver and the abdominal wall. Adhesions are therefore minimized, nor does the cystic duct catheter produce excessive ductal secretion of mucus which may be a cause of symptoms following use of a T-tube. An example of the clinical value of routine cholangiography through a cystic duct drain is seen in Figure 2*.

* In those patients in which this procedure is not possible due to advanced disease and in which the common duct is not opened, the following is of value. (This will be

DRAINAGE AFTER CHOLECYSTECTOMY



FIG 2—Female age 28 Cholecystectomy. No apparent indications present to explore the common bile duct. Routine catheter drainage of cystic duct which was so small that it had to be slit, before the catheter could be inserted. Cholangiogram made on the eighth day. Single cholesterol calculus clearly visualized, but only a very small portion of the supraduodenal portion of the duct is seen. The stone was removed before the patient was discharged from the hospital. Uninterrupted recovery. It can be well argued before the patient would have been removed. That is true but the fact remains that it was not, and that this patient would have gone back to her life of hard house work with the law of averages very much in favor of her having a future and a serious illness. This undoubtedly occurs in a large proportion of cases but in this instance it was prevented by routine cystic duct drainage. The occurrence was embarrassing for the writer but it was also very fortunate for both the patient and the surgeon.

uncommon because if the disease is so extensive that the cystic duct cannot be intubated, the ductal system will almost invariably be involved and demand active interference). The duct is injected with dye (diodrast) immediately before the abdomen is closed and approximately 10-15 minutes after the administration of morphine gr $\frac{1}{4}$. (The advantages and disadvantages of the use of morphine to the closed sphincter of Oddi are now under consideration. Undoubtedly, in some instances, it influences the contour of the terminal duct and consequently the interpretation of the pictures.) The patient is then taken to the Roentgenologic Department on the way to their room from the operating theatre, and a cholangiogram is made. The roentgenogram is thus taken very soon after the injection of the dye. This is, of course, dependent upon the condition of the patient, the distance to the X-ray rooms, the temperature of the passage-ways through which the patient must pass, and other factors.

The cystic duct tube can also be used for prolonged drainage and perfusion. The writer is among those who consider these methods of value, because he believes that *cholecystopathy which needs surgical treatment cannot be present without involvement of the entire biliary system*. But the most important factor is the determination of the presence or absence of common duct calculi, either on the operating table or as soon after as possible.

Technic of Cholangiography—Serial cholangiograms are necessary for correct clinical interpretations. Exposures are made after each injection of three cc of 35% diodrast (17.5 per cent has been found quite satisfactory in thin patients). Usually four or five injections are sufficient to fill the duct. If the duct is very large injections of five or ten cubic centimeters are used. Two more exposures are made at approximately two and ten minutes after the inhalation of amyl nitrite. By this method roentgenograms are taken during the filling and emptying phases. Thus, negative or positive shadows are more easily detected, and the constancy of their contour more definitely known. The latter is important in ruling out artefacts. All exposures before the duct is emptied should be made with the patient in the Trendelenburg position. In this way the liver radicals will fill more easily and the dye will not leave the duct until it overflows. Complete filling is, therefore, more likely. The evacuation roentgenograms (the emptying phase) are made in a partial Fowler's position.

CONCLUSIONS

Routine insertion of a small catheter into the cystic duct stump following cholecystectomy, for the purpose of performing cholangiography, is advocated. Thus, it can always be determined, in every patient, whether or not calculi remain in the common duct. The disadvantages of the procedure, to both patient and surgeon, are minimum, the advantages are maximum. The catheter also serves other purposes, for example, drainage, perfusion, if, and when, necessary, and possible dissolution or fragmentation of a calculus if one is found.

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INTESTINAL OBSTRUCTION DUE TO A GALLSTONE

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THIS REPORT of intestinal obstruction by gallbladder calculi is presented because of the clarity of roentgenologic demonstration and to add another verified case to the literature. Of the 36 cases previously recorded in which roentgenologic examination was made prior to operation, 22 revealed visualization of the biliary radicles. Although this sign was present on all the preoperative films, it was not recognized until after correlation with the operative findings.

Whenever gallstones have perforated through the gallbladder into the intestinal tract, there is usually a stoma sufficiently large to permit the reflux of intestinal or stomach contents into the gallbladder and biliary ducts. Since a barium meal is usually contraindicated in intestinal obstruction, the most common roentgenographic sign is the presence of gas in the gallbladder or hepatic system.

The following signs have been recognized roentgenologically

- 1 Air or contrast medium in the biliary tract
- 2 Complete or partial intestinal obstruction, as noted by distended loops of bowel
- 3 Visualization of the stone by a plain film, or by the ingestion of a barium meal, permitting the outlining of a radiolucent calculus
- 4 Change in position of a previously observed stone

Case Report—Hosp No 9467 M H, white, female, age 55, married, was admitted to the Memorial Hospital of Queens, Jamaica, N Y, April 13, 1942, with a history of upper abdominal pain and vomiting of six days' duration. The abdominal pain was constant, with intermittent exacerbations, and vomiting had become increasingly severe. The patient's health for the past few years had been generally poor, and she had been under treatment for hypertension, thyrotoxicosis, anorexia, and constipation, on various occasions. She had had a rather severe episode of abdominal pain and vomiting about ten years ago.

Physical Examination—The patient appeared critically ill, dehydrated, apparently in acute pain, and was vomiting dark brown material at frequent intervals. The abdomen was generally distended, tympanic, with a few distant borborygmi on auscultation. There was marked tenderness, with rebound pain, throughout the upper abdomen, but no evidence of rigidity or palpable masses. Temperature 97.2° F, pulse 140, B P 140/100, respirations 30. R B C 5,700,000, Hb 112%, W B C 11,250, with 81% polys. Blood sugar—200 mg, N P N—360, chlorides—300, Urine—1+ albumin, 4+ sugar, negative acetone, 2+ indican, and numerous granular casts.

* Captam, M C, U S Army

Immediate replacement therapy of fluids, proteins, chlorides, and vitamins was started intravenously. Gastro-intestinal intubation was instituted, with continuous suction. An initial plain film of the abdomen was taken, followed by the administration of a small amount of thin barium mixture through the tube, and serial roentgenograms were taken. After the roentgenologic examination the barium mixture was recovered by aspiration through the tube.

The patient's general condition improved under supportive therapy and, on April 16, 1942, celiotomy was performed through a right rectus incision. Exploration



FIG. 1.—Roentgenogram showing stomach filled with barium, and the cholecysto-duodenal fistula. The gallbladder is outlined by calculi, and the biliary radicles are delineated by the barium reflux.

revealed a round, obstructing calculus, the size of a large walnut, impacted, apparently, in the lower ileum. The proximal small intestine was markedly distended, atonic, but of good color. The ileum was incised longitudinally, and the obstructing calculus removed. The intestine was closed transversely, without diminution in the size of the lumen. There was almost immediate restoration of peristalsis in the distal bowel. Sulfanilamide was powdered about the site of the intestinal repair and into the general peritoneal cavity. The abdomen was closed without drainage.

The patient's postoperative convalescence was uneventful with the exception of

the passage of 14 faceted calculi per rectum during the 48 hours postoperative. The patient was discharged May 10, 1942 and has remained completely well to date.

Roentgenologic Report—The stomach revealed no intrinsic pathology. The duodenal cap was markedly dilated and the barium flowed into a small sac (the gallbladder) and then into the cystic duct and the hepatic radicles. The gallbladder was



FIG 2—Roentgenogram (five hour film) showing the great dilatation of the jejunum with the contained multiple, faceted, radiolucent calculi (arrows). The cholecystoduodenal fistula is clearly outlined as well as the stones in the gallbladder and the one in the common duct just proximal to the sphincter of Oddi.

firmly attached to the first part of the duodenum, and contained several radiolucent faceted shadows, significant of calculi. The upper small bowel was greatly dilated (Fig 1).

After five hours there was considerable gastric and duodenal retention of the barium. The gallbladder and ductal system, including two intrahepatic radicles, were clearly visualized as well. An oval, radiolucent stone could be demonstrated in the common

duct just proximal to the sphincter of Oddi. Above this, the common duct was dilated. The jejunum appeared three to four times its normal size, and contained approximately 11 faceted, radiolucent stones (Fig 2).

A 24-hour study revealed considerable gastric retention, and the remaining barium meal had progressed only slightly, and was still present in the upper small bowel. A



FIG 3—Roentgenogram (24 hour film) showing the distension of the proximal, small bowel, and the large calculus producing obstruction near the junction of the ileum and jejunum (arrows)

definite communication between the gallbladder and the duodenal cap was visualized at this time. In the right lower quadrant a large, oval, circumscribed shadow of decreased density, surrounded by a calcified rim of increased density was present. Proximal to this apparent calculus the small intestines were markedly distended and contained the numerous other calculi (Fig 3).

After a period of 30 hours, there had been no progress of the barium meal, indicating, apparently, a complete obstruction at a level of the proximal ileum. The large

calculus did not appear to have changed its position in comparison with the previous study (Fig 4)

At operation, the large calculus which produced the obstruction was removed. Figure 5 shows the calculus removed, surrounded by 15 faceted stones, which were passed per rectum.



FIG 4—Roentgenogram (30 hour film) showing the large calculus again visualized, with its outer, calcified ring (arrows)

SUMMARY

This report of an instance of intestinal obstruction due to gallstones, resulting from a cholecystoduodenal fistula, illustrated the value of an early diagnosis, determined roentgenologically. With the proper technic, and serial observations, it is possible, in many instances, to localize the exact point of obstruction for the surgeon. Furthermore, the utilization of intestinal intubation contributed materially to the management of this case.

(1) By enabling decompression of the intestinal tract preliminary to

definitive operative treatment of the obstruction, and (2) by permitting the administration of a small, thin barium mixture for roentgenographic identification of the nature and location of the obstructing agent, followed by the safe, easy removal of the barium mixture through the tube



FIG 5—Photograph, in the center of which is the large calculus removed at operation, which produced the obstruction and which is surrounded by the smaller faceted calculi which were passed per rectum following operation

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RESULTS OF GALLBLADDER SURGERY IN DIABETES MELLITUS

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SEVENTY-SIX diabetic patients have had gallbladder surgery in this clinic during the 16 years from 1926 through 1941. The incidence of gallbladder disease in the diabetic has been reported in several large series and no attempt will be made here to extend these data. On the other hand, little information has been formulated about the results of gallbladder surgery in the patient with diabetes. Because information about these 76 patients, both preoperatively and follow-up, is almost entirely complete, these data may be found valuable to the physician who advises operative treatment of gallbladder disease in the patient with diabetes, particularly in consideration of the question of (1) any greater operative risk, (2) of the effect that the operation may have upon the diabetes, and (3) of whether or not diabetes will tend to favor the persistence of biliary tract infection that would in a normal person subside.

The problem of adequate nutrition and dietary regulation for the diabetic, already somewhat of a task for both physician and patient, meets a substantial *impasse* with recurrent episodes of biliary colic and gastro-intestinal upsets, and it is the sick, bewildered patient, frequently in hypoglycemia or acidosis who waits for spontaneous relief but finally comes into the hospital for surgery.

Dr Leland S McKittrick performed the operations upon all the patients in this series except two. By virtue of a single operator, the error inherent in variation of approach and technic is avoided. The medical management has been in the hands of members of this clinic.

Classification of this series is made under the headings cholecystitis, cholelithiasis, choledocholithiasis, cholelithiasis with complications, infectious cirrhosis of the liver, and neoplasms of the gallbladder or pancreas. In Table I are the compiled data of the 76 diabetic patients who have had gallbladder surgery prior to January, 1942. Sixty-five are benign gallbladder disease, one is infectious cirrhosis of the liver, two are carcinoma of the gallbladder, and eight are carcinoma of the pancreas.

Analysis of the data in Table I show that 83 per cent of those coming to operation are women, the average age at operation is 58 years. The duration of diabetes before operation is from one month to 25 years for primary gallbladder disease, excluding carcinoma, the average duration of diabetes before operation is five years. The youngest patient is age 14. Two were operated upon at the age of 79, one of these (Case 40) is a man.

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who had diabetes for 23 years prior to the development of gallbladder symptoms, and he came to operation complaining of pain, nausea, vomiting and jaundice. A cholecystectomy and choledochostomy were performed, he had an uneventful recovery, there was never recurrence of his symptoms, and four years later he died at the age of 83 with pulmonary tuberculosis. The other patient (Case 45) who was operated at age 79 had symptoms of gallbladder disease which developed at age 71, concomitant with his diabetes, a cholecystectomy and choledochostomy were performed, and three years later, in January, 1942, at the age of 82, he was alive and asymptomatic.

Empyema, gangrene, hydrops of the gallbladder, biliary tract perforation and pancreatitis are included as complications of benign gallbladder disease. There are 14 patients (22 per cent) in this series who came to operation with such complications. Hydrops of the gallbladder appeared three times, empyema twice, empyema and gangrene of the gallbladder once, partial or free perforation of the biliary tract nine times. The operative mortality for the entire series is in this group of patients with gallbladder disease and its complications, except for one patient (Case 36), a 77-year-old man with common duct stones. Apart from the immediate mortality (14 per cent), the results in patients with complications are 100 per cent good for permanent relief of symptoms (one patient is exempt because follow-up information was not obtained at the time of writing this paper).

Perforation of the biliary system by calculi occurred in nine of 65 patients coming to operation without neoplasm, or 14 per cent. Five of the nine were partial perforations, four were free perforations. Three of the perforations were in acutely inflamed gallbladders. Three were in gallbladders with empyema. This relatively high incidence is in agreement with the well known fact that the diabetic patient cannot limit infection normally. Commonly quoted statistics in all biliary tract disease are one to three per cent perforation, in contrast to the 14 per cent in this series. Elason and McLaughlin⁸ quote, without mention of the presence or absence of diabetes, the incidence of perforation as 0.9 per cent to 2.5 per cent in 6,816 cases reported by five authors. In 775 gallbladder cases of Elason and McLaughlin there were 17 (two per cent) who perforated, one of these had diabetes. Heuer⁹ reports an incidence of 26 per cent perforation in acute cholecystitis in nondiabetic patients.

Operative mortality for the entire group is 3.9 per cent, for those with benign gallbladder disease alone it is 4.6 per cent, this includes acute and chronic cases and those with complications. McKittrick¹ has recently reported data on all his surgery in both diabetic and nondiabetic patients with nonmalignant gallbladder disease. The majority of these were operated upon at hospitals other than the New England Deaconess Hospital. Operative mortality in these cases was 6.2 per cent for 81 diabetic patients, and 3.1 per cent for 286 patients without diabetes. Rabinowitch² reports an operative mortality of four per cent in 50 diabetic patients with chronic gallbladder disease.

The results of operative treatment of nonneoplastic gallbladder disease in the diabetic patients reported in this series compare favorably with those in the nondiabetic. Complete relief of symptoms was obtained in 77 per cent, partial relief in 12 per cent, and no relief in 11 per cent. Those who were alive in January, 1942, had survived operation from one to 14 years, an average of five and one-half years, and, in 1942, their average age is 63 years. Those who survived operation but who were dead in January, 1942, from any cause, lived an average of six years after operation, and died at an average age of 70. Fowler³ reported, in 1933, the end-results in the operative treatment of 979 cases of gallbladder disease in nondiabetics, complete relief of symptoms was afforded in 81.8 per cent, partial relief in 10.5 per cent, and no relief in 7.7 per cent.

Of the 13 operative failures, nine, or 70 per cent, had demonstrable gallbladder stones and concomitant cardiac, psychoneurotic, or gastric symptoms, subsequent to operation, it is now conservatively estimated, that in six of these nine failures the primary complaint was extrabiliary in origin. Prognosis must be guarded for operative treatment in the diabetic who shows evidence indicating coronary heart disease. Five of the 13 failures in this series had arteriosclerotic or hypertensive heart disease which, in the light of subsequent findings on follow-up examinations, was clearly the chief source of the patients' complaints. Root, Bland, Gordon and White⁴ have shown that coronary occlusion in diabetics over age 50 is three to eight times that in the nondiabetic. With this in mind, one must pay particular attention to the cardiac status of the diabetic patient, and attempt to make proper evaluation of both the biliary and cardiac systems for determination of that part which each may contribute to the patient's symptoms. McKitt-trick⁵ states that he can see "no indication for surgery in the so-called cholecystitis without stones. Only once or twice in a surgeon's career does he see, at operation, true infection of the gallbladder in the absence of stones. Results following cholecystectomy in nondiabetic patients for so-called cholecystitis without stones are too uncertain to justify this procedure in the diabetic patient."

This study does not bear out the postulate that eradication of a diseased gallbladder will either heal or lessen the severity of the diabetes, as measured by the insulin requirement one year before and one year after operation, provided all else remains as constant as possible in the life's habits of this clinic's diabetic patients. Considering 56 patients who had benign gallbladder disease with calculi, and who are suitable for comparison, the average insulin requirement one year before operation, when it is likely that the stones and associated bladder changes were present, was precisely the same as that one year after operation, namely, 21 units.

One unusual case has been excluded from the averages because the degree of insulin resistance was so great during the period prior to operation, and immediately thereafter, that her case stands apart from the rest of the series and, therefore, has not been included in the averages. This

TABLE I
RESULTS OF GALLBLADDER SURGERY IN DIABETES MELLITUS

Case	Sex	Diagnosis	Operation	Age at Oper	Alive or Dead	Yrs	Duration of Diabetes, 1942 Yrs	Duration of Diabetes before Gb Symptoms Yrs	SYMPTOMS						INSULIN RE- QUIRE- MENT One Year	
									Before Operation			After Operation			Before Oper	After Oper
									Pain	Indigestion	Jaundice	Pain	Indigestion	Jaundice		
1	F	Cholecystitis	Cholecystectomy	70 d@	71	3	2	+	+	+	0	+	+	0		
2	F	Cholelithiasis	Cholecystectomy	42 a@	56	18	4	+	+	+	0	Occ ‡	0	0	15	15
3	F	Cholelithiasis	Cholecystectomy	43 a@	57	16	1	+	+	+	0	0	0	0	20	20
4	F	Cholelithiasis	Cholecystectomy	65 d@	74	12	3	+	+	+	0	0	0	0	12	12
5	M	Cholelithiasis	Cholecystectomy	42 a@	53	18	0	+	+	+	0	0	0	0	0	0
6	F	Cholelithiasis	Cholecystectomy	68 a@	70	22	indef	0	0	0	0	0	0	0	42	38
7	F	Cholelithiasis	Cholecystectomy	44 a@	58	21	7	+	+	+	0	0	0	0	0	0
8	F	Cholelithiasis	Cholecystectomy	60 a@	73	25	1	+	+	+	0	0	0	0	24	24
9	F	Cholelithiasis	Cholecystectomy	51 d@	55	9	0	+	+	+	0	?	?	?	20	?
10	F	Cholelithiasis	Cholecystectomy	63 d@	68	19	6	+	+	+	0	0	0	0		26
11	F	Cholelithiasis	Cholecystectomy	43 d@	50	9	2	+	+	+	0	0	0	0	0	0
12	F	Cholelithiasis	Cholecystectomy	42 a@	52	12	0	+	+	+	0	0	0	0	20	42
13	F	Cholelithiasis	Cholecystectomy	57 a@	69	17	2	+	+	+	0	0	0	0	40	40
14	F	Cholelithiasis	Cholecystectomy	53 a@	63	10	0	+	+	+	0	0	0	0	18	10
15	F	Cholelithiasis	Cholecystectomy	52 a@	54	17	15	+	+	+	0	0	0	0	25	28
16	F	Cholelithiasis	Cholecystectomy	56 a@	61	9	2	+	+	+	0	0	0	0	52	42
17	F	Cholelithiasis	Cholecystectomy	49 a@	52	8	5	+	+	+	0	0	0	0	0	0
18	F	Cholelithiasis	Cholecystectomy	48 a@	50	13	10	+	+	+	0	0	Occ	0	25	55
19	F	Cholelithiasis	Cholecystectomy	49 a@	57	9	0	+	+	+	0	0	0	0	28	8
20	F	Cholelithiasis	Cholecystectomy	60 a@	66	6	indef	+	+	+	0	0	0	0	16	12
21	F	Cholelithiasis	Cholecystectomy	52 a@	54	9	7	+	+	+	0	0	0	0	38	38
22	F	Cholelithiasis	Cholecystectomy	62 a@	62	9	8	+	+	+	0	0	0	0	0	0
23	F	Cholelithiasis	Cholecystectomy	74 d@	84	16	6	+	+	+	0	+	+	0	5	5
24	F	Cholelithiasis	Cholecystectomy	32 a@	37	13	indef	0	+	+	0	0	+	0	10	12
25	F	Cholelithiasis	Cholecystectomy	14 a@	25	12	0	+	+	+	0	+	+	0	26	38
26	F	Cholelithiasis	Cholecystectomy	56 a@	65	10	0	+	+	+	0	0	+	0	5	5
27	F	Cholelithiasis	Cholecystectomy	63 d@	65	14	5	+	+	+	0	+	+	0	5	5
28	F	Cholelithiasis	Cholecystectomy	63 a@	67	15	0	+	+	+	0	+	+	0	20	6
29	F	Cholelithiasis	Cholecystectomy	62 a@	67	5	2 mos	+	+	+	0	+	+	0	12	12
30	F	Cholelithiasis	Cholecystectomy	58 a@	63	12	6	+	+	+	0	+	+	0	12	12
31	F	Cholelithiasis	Cholecystectomy	66 a@	70	5	0	+	+	+	0	0	0	0	12	0
32	F	Cholelithiasis	Cholecystectomy	71 a@	72	23	1 mo	+	+	+	0	0	0	0	56	56
33	M	Cholelithiasis	Cholecystectomy and choledochostomy	65 a@	68	29	25	+	+	+	+	+	+	0	26	42
34	F*	Cholelithiasis	Cholecystectomy and choledochostomy	56 d@	65	15	5	+	+	+	+	0	0	0	20	15
35	F	Cholelithiasis	Cholecystectomy and choledochostomy	43 a@	45	9	6	+	+	+	0	+	0	0	40	42
36	M	Choledocholith	Choledochostomy	71 d@	72	7	4	+	+	+	+	0	0	0	12	12
37	F	Choledocholith	Choledochostomy	77	died	1	0	0	+	+	+	—	—	—	0	—
38	F	Choledocholith	Cholecystectomy and choledochostomy	69 a@	71	2	0	0	+	+	+	0	0	0	30	0
39	F	Cholelithiasis and choledocholith	Cholecystectomy and choledochostomy	60 a@	67	32	25	+	+	+	+	0	0	0	30	40
40	M	Cholelithiasis and choledocholith	Cholecystectomy and choledochostomy	79 d@	83	27	23	+	+	+	+	0	0	0	0	14

‡ Glossary "Occ" = occasional and not significant to the patient

* Operated upon by Dr D F Jones

GALLBLADDER SURGERY IN DIABETES

TABLE I—(Continued)
RESULTS OF GALLBLADDER SURGERY IN DIABETIC MILLITUS

Case	Sex	Diagnosis	Operation	Age at Oper	Alive or Dead	Duration of Diabetes Yrs	Duration of Diabetes before Gb Symptoms Yrs	SYMPTOMS						INSULIN RE- QUIRE- MENT One Year		
								Before Operation			After Operation			Before Oper	After Oper	
								Pain	Indigestion	Jaundice	Pain	Indigestion	Jaundice			
41	F†	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	61	d@	71	17	0	+	+	0	+	+	0	10	10
42	M	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	47	a@	56	13	0	+	+	0	0	0	0	0	0
43	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	71	d@	80	12	1	+	0	+	0	0	0	0	0
44	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	64	a@	76	18	0	+	+	+	0	0	0	20	40
45	M	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	79	a@	82	11 mo	+	+	0	0	0	0	0	0	0
46	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	49	a@	52	4	2	+	+	0	0	0	0	8	8
47	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	63	a@	65	18	2	+	+	+	0	0	0	10	10
48	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	57	a@	59	5	0	+	+	+	0	0	0	0	0
49	M	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	37	a@	40	12	1	+	+	0	+	+	0	67	120
50	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	84	a@	87	19	14	+	+	+	0	0	0	0	0
51	F	Cholelithiasis and Cholelithiasis	Cholecystectomy and Cholelithiasis	52	a@	57	8 4 mos	0	+	+	0	0	0	0	24	12
52	F	Cholelithiasis Hydrops of Gb	Cholecystectomy	54	died postop	8	1	+	+	0	—	—	—	24	—	—
53	F	Cholelithiasis Hydrops of Gb	Cholecystectomy	52	a@	53	10	9	+	+	0	0	0	0	60	48
54	F	Cholelithiasis Hydrops of Gb	Cholecystectomy	44	a@	47	7	1	+	+	0	0	0	0	40	50
55	F	Ac Cholecystitis and Cholelithiasis with partial perforation of Gb	Cholecystostomy	68	d@	70	20	5	+	+	0	0	0	0	24	24
56	F	Ac Cholecystitis and Cholelithiasis with perforation	Cholecystectomy and Cholelithiasis	58	a@	58	9 indef	+	+	0	0	0	0	16	8	8
57	F	Cholelithiasis, with partial perforation	Cholecystectomy	57	a@	59	9	7	+	+	0	0	0	0	56	20
58	M	Cholelithiasis, with gangrene of Gb & partial perforation	Cholecystostomy	63	d@	68	25	20	+	+	0	0	0	0	0	0
59	M	Cholelithiasis empyema & partial perforated Gb	Cholecystectomy	55	died postop	13	13	+	+	0	0	0	0	0	0	16

† Operated upon by Dr. Frank H. Lahey

TABLE I—(Continued)
RESULTS OF GALLBLADDER SURGERY IN DIABETES MELLITUS

Case	Sex	Diagnosis	Operation	Age at Oper	Alive or Dead	Duration of Diabetes 1942 Yrs	Duration of Diabetes before Gb Symptoms Yrs	SYMPTOMS						INSULIN REQUIREMENT One Year	
								Before Operation	After Operation	Before Operation	After Operation	Before Operation	After Operation	Before Oper	After Oper
60	Γ	Cholelithiasis empyema & gangrene of Gb with perforation	Cholecystostomy	58 a@	63	21	9	+	+	0	0	0	0	24	24
61	F	Cholelithiasis empyema & partial perforation Gb	Cholecystostomy	78 a@	84	7	1	+	+	+	0	0	0	0	0
62	F	Cholelithiasis with perfor & abscess	Choledochostomy	61 d@	69	12	indef	+	0	0	0	0	0	0	0
63	M	Ac Cholelithiasis choledocholithiasis, with perforation	Cholecystectomy and Choledochostomy	69 d@	72	5	2	0	+	+	0	0	0	18	12
64	F	Cholelithiasis and sub ac pancreatitis	Cholecystectomy and Choledochotomy	73 d@	73	18	0	+	+	+	?	?	?	15	—
65	F	Cholelithiasis and sub ac pancreatitis	Cholecystectomy and Choledochotomy	56 a@	63	23	16	+	+	0	0	0	0	22	22
66	M	Cirrhosis of liver infectious	Cholecystogastrotomy	52 a@	65	16	indef	0	+	+	0	0	0	0	0
NEOPLASTIC															
67	Γ	Carcinoma of Gb & cholelithiasis	Cholecystectomy and Choledochostomy	55 d@	58	4	3 mos	+	+	+	20 mos	0	20 mos	0	0
68	M	Carcinoma of Gb and cholelithiasis	Cholecystostomy and Choledochostomy	66 a@	69	3	0	0	+	+	0	0	31 mos	12	16
69	F	Carcinoma of pancreas and cholelithiasis	Cholecystostomy	52 d@	53	7 mos	1 mo	+	+	+	+	+	?	42	?
													Died 7 mos after onset symptoms		
													Died 11 mos after onset symptoms		
70	F	Carcinoma of pancreas and cholelithiasis	Cholecystogastrotomy	68 d@	69	2	9 mos	0	+	+	6 mos	7 mos	8 mos	30	18
71	F	Cholelithiasis with ? carcinoma of pancreas	Cholecystostomy and Choledochostomy	69 a@	69	1	1	0	0	+	0	0	0	28	20
													Postoperation—6 mos		
72	F	Carcinoma of pancreas	Cholecystogastrotostomy	64 d@	65	1	8 mos	0	+	+	?	?	0	—	—
													Died 5 mos after onset symptoms		
													Died 24 mos after onset symptoms		
73	F	Carcinoma of pancreas	Choledochoduodenostomy	45 d@	47	30 mos	8 mos	+	0	+	10 mos	?	16 mos	25	16
74	F	Carcinoma of pancreas	Choledochoduodenostomy	58 d@	58	2	1	+	+	+	3 mos	3 mos	5 mos	15	?
													Died 9 mos after onset symptoms		
75	M	Carcinoma of pancreas	Cholecystogastrotostomy	67 d@	68	10 mos	4 mos	+	+	+	?	?	?	15	?
													Postoperation—8 mos		
76	F	Carcinoma of pancreas	Cholecystogastrotostomy	70 a@	71	1	6 mos	0	0	+	0	0	0	—	—

patient, a woman of 64 years (Hosp No 19110), developed insulin resistance during the five months preceding operation for common duct stones, when she had jaundice constantly, such that she required 300 to 400 units of insulin a day before operation and actually required 1000 units of insulin each day during a brief period following operation. However, during the next month, the insulin requirement rapidly declined, and two years after operation she was sugar-free, with normal blood sugars, without any insulin whatsoever. Although we cannot dismiss the influence of chronic jaundice and obstruction by stones in the common duct in producing this extraordinary degree of insulin resistance, the exact relation between the jaundice and the insulin resistance is not entirely clear.

The question has often been raised whether patients who suffer jaundice either because of toxic damage to the liver or infectious hepatitis are likely later to develop diabetes. In clinical experience it is sometimes difficult to relate jaundice to diabetes, especially since cases of cirrhosis of the liver with jaundice not uncommonly show a remission of the diabetes. Glucose tolerance curves will often show curious divergences during jaundice, some being low and some showing elevations of the diabetic type. Raab and Strauber⁶ compared the glucose tolerance curves of 12 normal persons, 12 diabetics and 10 patients with parenchymal jaundice. They showed that both after glucose and after adrenalin, the blood sugar response in diabetes and parenchymal jaundice are similar. Soskin, Allweiss, and Mirsky⁷ demonstrated that in a depancreatized dog receiving a constant injection of insulin plus dextrose, just sufficient to maintain the blood sugar at a constant level, the dextrose tolerance curve becomes definitely diabetic in type after administration of diphtheria toxin, then interpretation is in terms of liver function with toxemia.

One patient (Case 66) with a clinical and laboratory diagnosis of diabetes developed jaundice and gastro-intestinal complaints which warranted operative treatment. Exploration revealed no primary biliary tract disease, but an infectious cirrhosis of the liver. A cholecystogastrostomy was performed, and since then he has been asymptomatic. His diabetes has never been severe enough to require insulin either before or following operation, and in January, 1942, 13 years after his operation, he has gotten along well on dietary regimen alone. One would question that this man had true diabetes. The point to emphasize is restatement of the fact that a diagnosis of true diabetes in association with what is apparently gallbladder disease should not be accepted unless glycosuria and persistent hyperglycemia are present.

If it is true that jaundice is likely to affect the severity of diabetes or to cause diabetes then it should be true that patients in this series of gallbladder cases, who have had jaundice on one or more occasions, should show in the later course some evidence of this effect. There are 15 patients in this series who were jaundiced one or more times before operation, and who are subjects for comparison of their insulin requirements one year before and one year after operation. Like those who did

not show jaundice, these 15 patients required on the average, no more or no less insulin before operation than after operation, namely, 14 units. This total average insulin dose is considerably smaller than that required for those who were not jaundiced (14 units *versus* 21 units) and represents, on the whole, a group with less severe diabetes than those without jaundice.

Cholecysto-enterostomy, with carcinoma of the head of the pancreas, and removal or drainage of the gallbladder, with a neoplasm of that structure, afforded palliation not only of jaundice but frequently also of pain for as long as three to ten months in carcinoma of the pancreas head, and even longer in carcinoma of the gallbladder. The diabetic's course in this respect is essentially no different from that of the non-diabetic. Five patients with carcinoma of the pancreas who were operated upon for release of common duct obstruction and who were dead in January, 1942, lived an average period of 11 months after the first appearance of symptoms referable to that disease.

CONCLUSIONS

1 The result of surgical treatment of gallbladder disease in the patient with diabetes is equally as good as in the patient without diabetes.

2 Complete relief of symptoms was afforded in 77 per cent of 65 cases with benign gallbladder disease, partial relief in 12 per cent, and no relief in 11 per cent.

3 Operative mortality for the entire series, including benign and malignant lesions, is 3.9 per cent. For those with benign gallbladder disease, including acute and chronic lesions and complications, the operative mortality is 4.6 per cent.

4 The eradication of a diseased gallbladder will neither heal nor lessen the severity of diabetes, as measured by the insulin requirement one year before, as compared with one year after operation.

5 The presence or absence of jaundice in the diabetic patient with benign gallbladder disease does not affect the severity of the diabetes subsequent to successful operation.

6 The incidence of complications in benign gallbladder disease is considerably greater in the diabetic than in the nondiabetic. Twenty-two per cent of the benign gallbladder lesions came to operation with complications which included hydrops, empyema, gangrene, perforation and pancreatitis. Except for the immediate operative mortality in the group (14 per cent), the result of surgical treatment was excellent.

7 Perforation of the biliary system by calculi occurred in 14 per cent of all patients with benign gallbladder disease coming to operation. Two-thirds of the perforations were in acutely inflamed or empyemic gallbladders.

8 The patient with gallstones should be "operated upon when the conditions of time, place, surgeon and physician are propitious." The indication for operation must be based upon the dangers incident to gallstones in the

nondiabetic, the greater susceptibility to perforation and the greater liability to arteriosclerosis in the diabetic

9 The indication and results of surgical treatment of the diabetic patient with an obstructive malignant lesion of the gallbladder or pancreas, is essentially the same as in the patient without diabetes. Marked diminution in insulin requirement will sometimes be seen in patients with these lesions, and in obstructive jaundice following operative release of the obstruction

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ABSORBABLE COTTON, PAPER AND GAUZE*

(OXIDIZED CELLULOSE)

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FOR AT LEAST THIRTY YEARS, in the Department of Surgery of Columbia University, there has been a continuing interest in the possibility of finding a relatively nonirritating, absorbable material. Many chemical products were tested, but few offered enough promise to justify further investigation. Recently (1935) Dr Hans Clarke, of the Department of Biochemistry, suggested polyvinyl acetate, which proved nonabsorbable in its fully esterified condition and too irritating after partial or complete hydrolysis. In 1941, he proposed a trial of oxidized cellulose which had just been prepared by Kenyon, and his collaborators^{2, 3} (U S Pat No 2,232,990), Eastman Kodak Research Laboratories†

The experiments here described, though less extensive than could be desired, are now reported, in view of the interesting and important results secured with the same material by Dr Tracy J Putnam,⁴ of the Department of Neurology.

To the surgeon it is of some interest whether such a product is in the form of cotton, gauze or paper. The material first investigated was in the form of cotton, later, some oxidized paper, prepared by the same method, was secured, also through the kindness of Dr Kenyon. This was in response to our desire for a nonirritating absorbable membrane which might be used to fill defects in such mesodermal structures as tendon sheaths and blood vessels. The cotton naturally suggested the possibility of hemostasis with a packing which would not have to be removed. This idea has been further extended to embrace oxidized gauze.

The introduction of these materials into the tissues of animals was, therefore, undertaken. The product used had been prepared by oxidizing long-fibered cotton with nitrogen dioxide for seven hours. It had the appearance of ordinary surgical cotton, slightly off white, and somewhat more friable. It was, as reported by Yackel and Kenyon,² soluble in dilute aqueous alkalis because of extensive carboxyl group formation during oxidation. It was, therefore, thought that the product should also be capable of gradual dissolution in the tissue fluids in contact with relatively undamaged tissue. It did not withstand sterilization in the autoclave, but it kept its tensile strength when boiled in water for three minutes. The sterilization so obtained

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† The writer wishes to express her appreciation of the information regarding this substance communicated by Dr Kenyon, in advance of publication (1942)

is obviously not enough for use in human surgery, since spores would not be destroyed by this method, but if the material should prove useful this difficulty might be overcome, possibly by preparation and packing under sterile conditions

Ten samples of oxidized paper were available a year later. These had been oxidized (A) 1 hour, (B) 2 hours, (C) 3 hours, (D) 4 hours, (E) and (F) 5 hours, (G) 21 hours, (H) 29 hours, (I) 45 hours, and (K) 69 hours. The longer the oxidation the greater was the shrinkage of the paper from its original size, the greater the brittleness and surface glazing and the less the tensile strength, although the fiber structure was grossly maintained. Microscopically, however, possibly through further degradation in the process of paraffin embedding and staining, the fibers of the cotton and gauze do not have the usual glassy appearance with central canal seen in unoxidized material, but appear as homogeneous eosinophilic bands, difficult to distinguish from coagulated protein.

Preliminary experiments suggested that the more highly oxidized samples, which were more acid, were more irritating to the tissues and as after boiling, these samples tore very readily when wet, sample H, I and K were soon discarded. Sample G 21-hour oxidation was used in the first series, since it was thought that the less oxidized samples might not be absorbed. Later, however, through a chance selection it was found that sample D was absorbed and this after only four-hours oxidation, had considerably more tensile strength than sample G. The papers kept for a year at room temperature in the laboratory continued to change slowly, and samples G through K at the end of that time were so brittle and parchment-like that they could no longer be used.

In the first group of experiments the cotton, seven-hour oxidation, was introduced into the abdominal muscles of cats and dogs. This, as was the case in all of the procedures, was done with the animal under nembutal anesthesia, and with strict asepsis maintained. The abdomen was opened through a right rectus incision, and the parietal peritoneum over the transversalis exposed by gentle retraction. It was then incised, and a pocket made in the muscle by blunt dissection. The sample, a fragment about $4 \times 3 \times 2$ mm, was introduced. The pocket was closed by a black silk suture in the peritoneum and fascia, placed at some distance away from the implanted cotton. The implantation was also as far as possible from the incision in the abdominal wall, to avoid risk of skin contamination. Some of the animals employed were those used in the introductory course in Second Year Surgery, and had, in addition to the deliberate introduction of the experimental foreign bodies, other procedures in the abdominal cavity. These, however, were clean operations. Nevertheless, the danger of contamination in this group was considered greater than in those done without the presence of numerous observers and with unskilled assistance. The results are shown in Table I. It will be seen that in eight cases, at and after four weeks, the cotton was absorbed, with varying degrees

TABLE I
OXIDIZED COTTON IN MUSCLE—SEVEN-HOUR OXIDATION

S P No	Days	Absorption		Reaction	Comment
		Gross	Microscopic		
20121	4	0	0	0	Animal dying
20129	9	0	0	Polys Mild	
20050	14	±	±	F B Mild	
19093	28	+	+	Scar tissue	Class *
19094	28	+	±	F B Very mild	Class Tiny fragments microscopically
19095	28	+	+	Polys Abscess	Class Abscess around suture
19096	28	+	+	Polys Intense	Class Abscess around suture
19110	28	+	+	Polys Intense	Class
19112	28	+	+	F B Mild	Class Polys around suture
20613	35	+	+	Scar tissue	Suture in scar
20614	35	+	+	F B Moderate	

of foreign body reaction and phagocytosis. Solution, in the true sense, is likely to be retarded in the presence of damaged tissue, where the buffering power of the fluids is reduced. The lack of reaction in the four-day test (Fig 1) was thought probably due to the fact that the animal was failing steadily and perhaps was unable to produce any tissue response to the irritant.

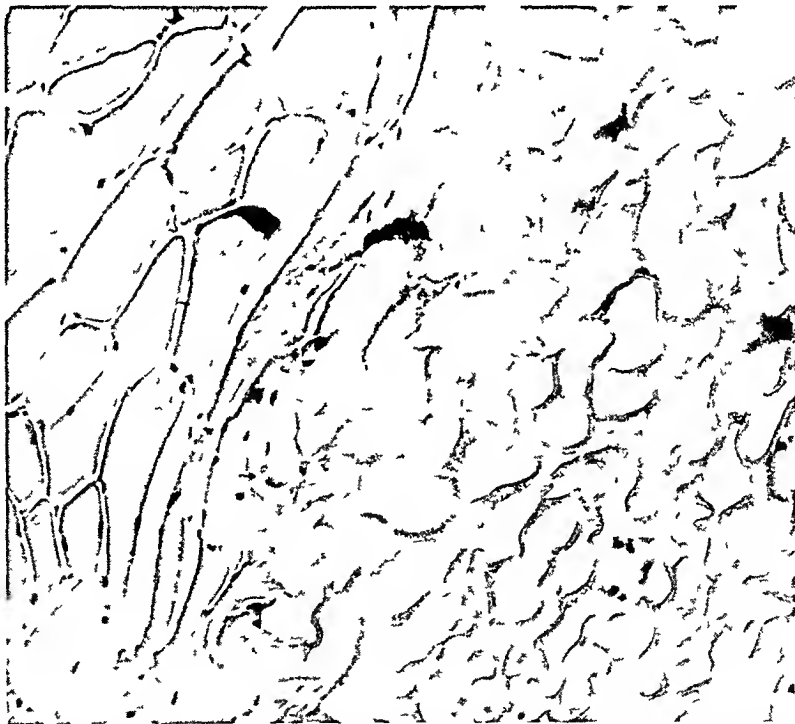


FIG 1—S P No 20121. Photomicrograph. Oxidized cotton in muscle, four days. No reaction. This shows the appearance of the material when it has not been altered by the tissues, but after paraffin embedding, sectioning and staining.

In one case, S P No 19094, a few microscopic fragments were found surrounded by giant cells. In the 14-day case there was partial absorption grossly and microscopically. There was in every case difficulty of distinguishing between a tissue reaction which might have been due to the cotton and that obviously expected from the presence of the black silk suture. The

* Where "Class" appears in Tables I and II, it refers to an animal used in class instruction.

suture was, of course, necessary for two reasons. First, to insure the sealing of the material in the pocket in the muscle, and, second, to mark the site.

The paper which was introduced into the muscle was sample G, oxidized 21 hours. Four of these animals were those in which the cotton had been introduced on the opposite side. It will be seen from Table II that in all but two of the seven implantations the paper was absorbed. The first case was that of the animal who lived only four days. The other was one of three animals, used also for class study, and sacrificed at the end of 26 days. The bulk of the material had been absorbed in this case, and what remained was microscopically fragmented. The nine-day absorption was a surprise, and it is possible that the wrong plane of section may have been taken, since the paper was very thin. None was seen grossly, however, on transillumination.

TABLE II
OXIDIZED PAPER IN MUSCLE—21-HOUR OXIDATION

S P No	Days	Absorption		Reaction	Comment
		Gross	Microscopic		
20121	4	0	0	0	Animal dying
20129	9	+	+	F B Mild	
20150	14	+	+	F B Very mild	
20342	26	+	+	F B Mild	Class Polys around suture
20343	26	±	0	F B Mild	Class F B reaction around suture
20344	26	+	+	F B Mild	Class
20613	35	+	+	F B Very mild	

Further detailed work is obviously desirable to determine as nearly as possible the usual absorption time, but it is clear that the material is absorbed and that it excites a foreign body reaction which is not necessarily excessive. Again, it should be emphasized that the more the tissue damage, by operative trauma or bacterial action, the greater the inflammatory reaction and possibly the retardation of true solution of the material in the less alkaline medium.

The next tissue investigated was brain, with the idea of the possible value of the cotton in hemostasis. We are indebted to Dr. James G. Galbraith for the meticulous care with which he introduced this material into the parietal lobes of cats. Through a midline incision in the shaved scalp the right temporal muscle was retracted and a trephine opening was made in the right parietal bone. This was enlarged by rongeur to 1.5 cm. in diameter. A linear incision was then made in the dura over the posterior part of the cerebral hemisphere and, with a bayonet forceps by blunt dissection, the cortex was split. A No. 19-gauge cannula was introduced into the brain, anteriorly and medially, to a 15-mm. depth, and a small bit of oxidized cotton, 4 × 3 × 2 mm., was expressed into the subcortical white matter. The dura was closed by interrupted, fine silk sutures, and the wound in layers with interrupted silk. One case was controlled by also introducing, somewhat posteriorly, a piece of temporal muscle of about the same size as the cotton.

The results of these experiments may be seen in Table III. In S P Nos. 21218 and 21219 the cotton had been soaked in soluble thrombin⁴ provided

TABLE III
OXIDIZED COTTON IN BRAIN—RIGHT PARIETAL LOBE—SEVEN HOUR OXIDATION

S P No	Days	Absorption		Reaction	Comment
		Gross	Microscopic		
20576	10	±	0	Γ B Mild	
21326	18	+	±	Γ B Intense	
21327	18	±	±	Γ B Intense	
21320	21	±	0	Polys Necrosis	
21321	21	+	±	Γ B Mild	
20698	42	+	+	Γ B Mild	
21218	43	+	+	Inflam Trace	Soaked in thrombin Muscle control *
21219	43	+	+	Γ B Trace	Soaked in thrombin

by Dr Tracy J Putnam of the Department of Neurology. In these two cases there was less reaction to the damage than in any of the others. Both were 43 days after operation. It will be seen that in all instances there was some tissue reaction (Fig 2), but this was mild in five out of eight, and was also elicited by the muscle implant. Absorption was incomplete at ten days. All three six-week cases showed complete absorption. In the 18- to 21-day period there was some variation. Unfortunately no four-week cases were done in this group, but it can be said that the material is absorbed in the brain some time between three and six weeks, is not unduly irritating, and provokes a minimum of glial reaction. All these animals recovered well from the procedure after a few days of lethargy, and showed no focal nor general signs immediately before autopsy.

In five instances oxidized paper was tested in relation to the dura. Four



FIG 2—S P No 20698. Photomicrograph. Oxidized cotton in brain, 42 days. None of the material remains. No polymorphonuclear leukocytes present. A few hemoglobin-laden phagocytes and slight glial proliferation.

* Muscle Implant Control. Muscle had been absorbed. Reaction the same as to the paper i.e. hemosiderin in phagocytes, slight glial proliferation, no multinucleated giant cells.

TABLE IV
OXIDIZED PAPER—SUBDURAL
Absorption

S P No	Days	Size in Mm	Hours Oxidation	Absorption		Reaction	Comment
				Gross	Microscopic		
20697	42	10 x 10	21	+	+	F B Mild	
21218	43	5 x 5	4	+	+	F B Mild	3 mm gap in closure, dura
21219	43	5 x 5	4	+	+	F B Mild	
OXIDIZED PAPER—EPIDURAL							
21327	18	2 x 5	4	±	±	Abscess	Bone wax
21321	21	2 x 5	4	+	±	F B Mild	

of these animals were those in which the cotton pledget had also been put in the brain. In three cases the paper was placed on the surface of the brain twice over the puncture wound at the site of the cotton introduction, and once on the uninjured surface. The dura was then closed over the material with fine interrupted sutures. In two cases the paper was placed on the surface of the dura over the opening which had not been sutured, thus making the closure in the wound. In both of these cases the animal also had the brain wound.

As will be seen in Table IV no paper was found in the three cases where



FIG 3—S P No 21218 Photomicrograph Oxidized paper, subdural, 43 days. No material remains. Few phagocytes present.

it had been placed between the brain and the dura. The incision in the dura was cleanly healed, there was no adhesion between the brain and the dura, and both surfaces were smooth and glistening. The disappearance was grossly complete. Microscopically, there were no polymorphonuclear leukocytes present and no multinucleated giant cells, but there were phagocytic mononuclear cells in the dura, often laden with hemosiderin (Fig 3).

In the two cases where the dura had not been closed, and the paper placed over the defect, there was clean wound healing in one, but in the other there was an epidural collection of thick reddish-brown exudate in which gross particles of bone wax were seen. Microscopically, no paper was recognized in either of these instances, but there was a foreign body

TABLE V
OXIDIZED PAPER IN KNEE JOINT—FOUR-HOUR OXIDATION

S P No	Days	Size in Mm	Absorption		Reaction	Comment
			Gross	Microscopic		
21326	18	5 x 3	+	+	F B Mild	Trichinae
21327	18	5 x 3	+	0	F B Mild	
21320	21	5 x 3	+	+	F B Very mild	
21321	21	5 x 3	+	+	F B Very mild	

reaction which might have been due to the material, but also might have been associated with the bone wax. The repaired deep surface of the dura was smooth, however, and there were no adhesions between this and the brain. Since, microscopically, some foreign body reaction was found in all these wounds of the dura, it is not possible to say that the paper disappeared by true solution. However, in no instance was it so irritating that adhesions formed between the dura and the brain.

Because of our original hope of finding something to use as a non-irritating membrane for repair of tendon sheaths, and because of the dif-



FIG 4—S P No 21327. Photomicrograph. Oxidized paper in knee joint, 18 days. A fairly intense inflammatory reaction to the suture is seen in the upper portion of the photomicrograph, and a mild foreign body reaction to the paper in the lower portion.

ficulty of testing this out in animal tendon sheaths, the knee joint was used to determine the effect of the material on synovial tissues. The animals used were those who had also had, at the same operation, the craniotomy. This made them unusually suitable for joint surgery, since, for the first few days after operation, their lethargy caused them to avoid undue use of the extremity. The knee joint was opened through a lateral incision, and a strip of paper, sample D, four-hour oxidation, 4 x 2 mm, was introduced into the suprapatellar bursa. An effort was made in closing the defect with three interrupted eye silk sutures, not to place these in the synovial

membrane, but just outside. The skin was closed with four interrupted black silk sutures. As will be seen in Table V, at autopsy, in the first 18-day case no trace of the foreign body was found free in the joint where it had been placed, nor in the tissues outside. The joint lining was smooth, glistening and not injected, and the sutures lay well outside the cavity. There was, microscopically, a mild foreign body reaction but no evident paper fragments. An incidental finding was the presence of minute encysted trichinae larvae. In the second 18-day case there was, just to the lateral

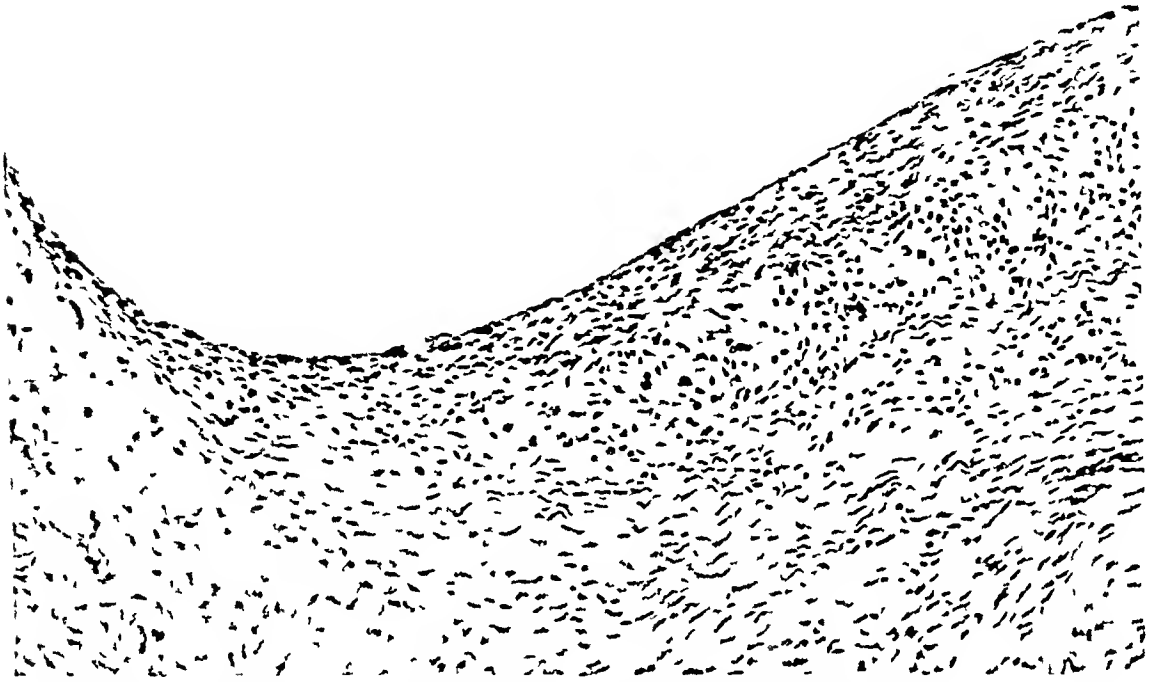


FIG 5—S. P. No. 21321. Photomicrograph. Oxidized paper in knee joint 21 days. There is slight thickening of the synovia, with a few lymphocytes and phagocytic cells.

side of the upper portion of the patella, an oval, slightly elevated pink zone, 6 x 3 mm. Otherwise the joint lining was smooth and glistening, without injection. There was no exudate. Microscopic examination of the red zone showed a localized mass of the material with a mild foreign body reaction, less intense than that around silk sutures in the same preparation (Fig. 4). In the two 21-day cases the knee joint showed no gross signs of inflammation and only a trace of foreign body reaction microscopically (Fig. 5). No material was found. In these four instances, at least, therefore, we have no evidence that the material causes undue inflammatory response in the joint such as might be followed by adhesions.

Oxidized cellulose in the form of gauze was then investigated. The shrinkage of this material is shown in Figure 6, and it is interesting that the texture of the oxidized samples is smoother and more silky than the original gauze, and, naturally, with the shrinkage, finer meshed. The 16-hour sample, however, was quite friable, and was only used once. The procedure was to deliver the omentum through a right rectus incision, onto warm moist pads. A square of gauze, 12 cm., was then laid on the surface, the omentum

TABLE VI
OXIDIZED GAUZE ON PERITONEAL SURFACE

S P No	Days	Hours Oxidized	Absorption		Reaction	Comment
			Gross	Microscopic		
21364B	6	7	±	0	Polys Intense	Second trauma
21364A	7	7	+	±	Polys Intense	More reaction to suture
21329	11	7	+	+	F B Moderate	
21347	14	16	+	+	F B Mild	
21102	20	7	+	+	F B Trace	

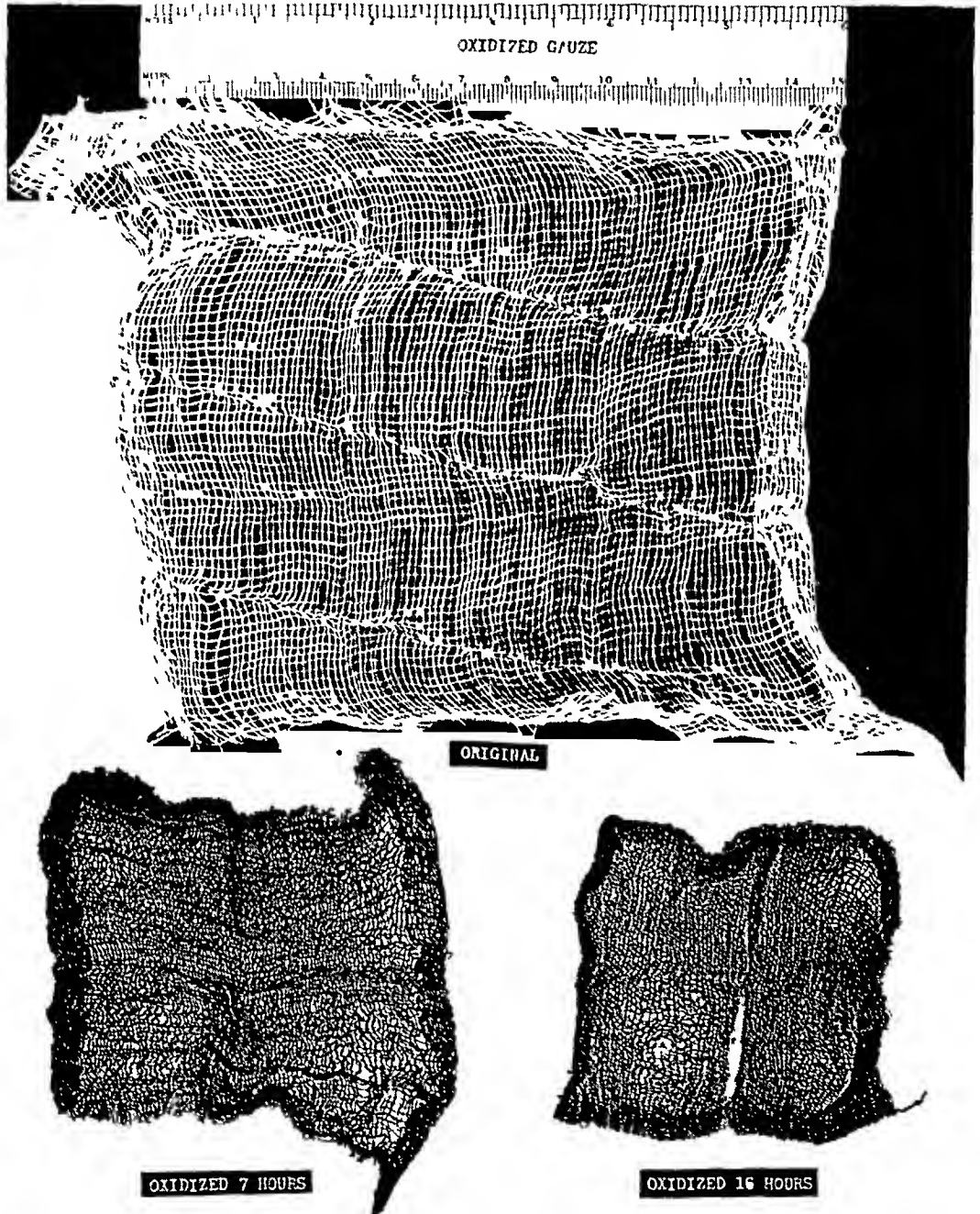


FIG 6—Photograph of three samples of gauze, all originally approximately the same size. Shrinkage following oxidation is illustrated.

folded over it, and tacked down with silk sutures which did not pass through the material. In the 11-day case the sutures used were a thread unravelled from the edge of the gauze itself. The results are shown in Table VI. The first case listed, six-days, is the same animal as the seven-day experiment. An exploratory operation was performed, seven days after the first procedure. The omentum was found to be thickened in the neighborhood of the marking sutures. This portion was amputated, after suitable hemostasis had been secured by ligature and a second piece of gauze, rolled this time instead of flat, was placed in the folded, already traumatized omentum. On reexploration at six days much greater thickening was found than previously but there were no other signs of inflammation about the gauze. Around the ligatures, however there was redness as well as swelling. The gauze appeared as a sticky light brown fluid and semi-

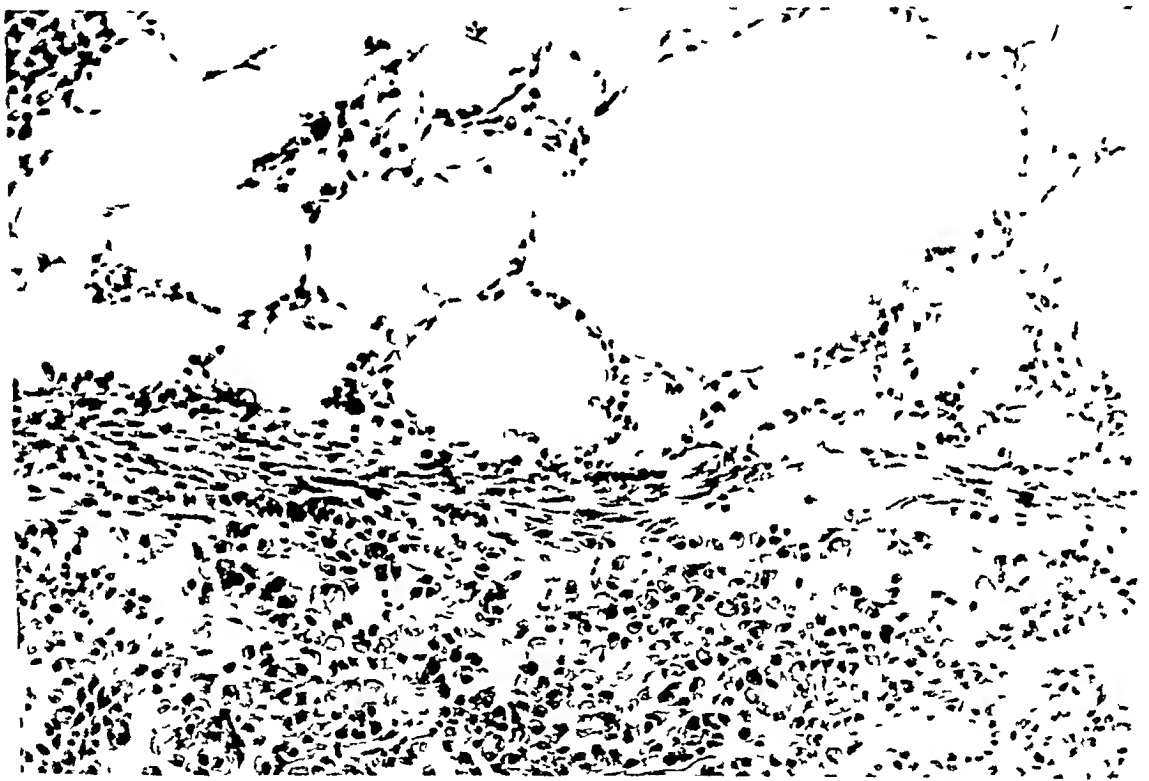


FIG 7—S. P. No. 21329. Photomicrograph. Oxidized gauze in omentum, 11 days. No material remains. Mononuclear and multinuclear phagocytic cells are seen and some foamy fat cells.

solid material lying in a smooth cavity. Microscopic examination showed an intense inflammatory reaction both to the foreign body and the ligatures, with polymorphonuclear leukocytes present in each case. More dilated blood vessels were seen about the sutures than about the gauze. At 11, 14 and 20 days no gauze remained. There was thickening in the omentum in each case, but no more inflammatory reaction than might have been expected from the operative trauma and the sutures (Fig. 7).

SUMMARY

Oxidized cellulose in the form of cotton, paper and gauze was found to disappear in muscle, brain, dura, joint and peritoneum of dogs and cats.

Control experiments of unoxidized material were not made because of the universal experience that gauze and cotton are not absorbed, and our familiarity with the reaction of the tissues to these materials

In all but one instance there was some tissue reaction, and in this case the cotton was not absorbed. How much the disappearance of the material is due to true solution and how much to solution after digestion by phagocytes it is not possible to say. Not much proliferation of connective tissue, nor of glia was found. No adhesions were formed between the dura and the brain or within joints.

CONCLUSIONS

A relatively nonirritating foreign material, oxidized cellulose, has been tested. It is hoped that, after further observations to determine the oxidation time associated with the most favorable properties, this may be employed in hemostasis and possibly in protecting injured surfaces where a smooth membrane is desired in the final healing. For this latter use further work must be undertaken to determine the length of time the material maintains its physical properties in the tissues when it is interposed between two surfaces where adhesions are to be avoided.

The length of time of oxidation may well be related to the rapidity of absorption. A method of sterilization must be developed so that all danger of spore contamination is avoided, and the desirable physical properties of the material are not altered. It is suggested by earlier experimental work with celloidin in this laboratory by W. C. Clarke,¹ in 1916, that some of the reaction observed with samples of the new material may have been due to contact with the skin of the investigators. The material was handled to a considerable extent before it was boiled for use, and epithelial debris may have adhered to it. New samples, not fingered except with gloves, will be tried. The degree of irritation to the tissues from any cause, however, does not seem to be extreme, and is usually less than that from the nonabsorbable sutures so freely used in plastic work.

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THE USE OF THROMBIN ON SOLUBLE CELLULOSE IN NEUROSURGERY

CLINICAL APPLICATION
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PREPARATION OF THROMBIN—The preparation of a relatively pure thrombin has been a recognized laboratory procedure since the work of Mellanby,¹ in 1933. His method has been greatly improved by Seegers,^{2, 3} who, with his collaborators, has reported on its use in experimental surgery. The hemorrhage from a fresh incision across the surface of the liver or brain was controlled by a spray of the solution. Similar results have been reported by Loznei, *et al*,⁴ with the use of rabbit thrombin, prepared by iso-electric precipitation. These investigators found the application of moist pledgets to be more effective than a spray of the liquid preparation. As far as I am aware, the first attempts to use such a preparation for neurosurgical purposes were made by Karr and Ziff⁵ at this institution. They prepared fresh thrombin from human plasma by a simple technic, and this proved of some value in cerebral surgery. According to the daily papers, a preparation of thrombin has been used by the Russian surgeon Kudryashev, but no references are available at present.

Preparations of thrombin which are highly active are now being manufactured according to the method of Seegers, and are, of course, far more convenient than the freshly prepared material. The thrombin comes in the form of a dry powder, easily soluble in water. A "clotting globulin" is also available, made from rabbit plasma. A globulin with thrombic activity, and a concentrated fibrinogen are being prepared on a large scale from human plasma.

The difficulty with fluid preparations has been that of application. The clot which is formed in less than a second with flowing blood is apt to be washed away before it can adhere, even though the flow is no more than an ooze. If the thrombin is applied upon pledgets of cotton, satisfactory hemostasis is secured under even adverse conditions, but hemorrhage usually begins at once if the pledget is removed.

By a fortunate coincidence, a new type of oxidized cellulose became available within recent months. The details of preparation of this material have been described by Yackel and Kenyon,⁶ and Unruh and Kenyon,⁷ and its properties are easily observed and of great interest. Physically, it resembles cotton wool. It will, however, slowly dissolve in slightly alkaline fluids. Frantz⁸ has carried out experiments which show that it is absorbed from various tissues of experimental animals (including the brain) with practically no inflammatory reaction. This prepared cellulose disintegrates upon autoclaving. It may, however, be boiled for three minutes or kept in 70 per cent alcohol until needed.

An obvious next step was to use this material saturated with thrombin solution. Tiny pledgets, measuring approximately $20 \times 5 \times 2$ mm were prepared by teasing out and folding the wet cotton. They were kept in 70 per cent alcohol. When needed they were dried at the time of

A



B

FIG 1—A Constant, profuse oozing from dural veins (arrows). Note pool of blood along edge of bone at bottom of picture.

B Hemorrhage controlled and wound clean, two minutes after application of thrombin on soluble cellulose (arrows). The pool of blood has been removed, and now has reaccumulated.

operation, and dampened with thrombin solution, so that each contained approximately 500 units. (It is possible that less would suffice.)

The most effective way of using these pledgets was found to be to tampon a bleeding point with moist cotton, and suck the latter dry. The pledget containing thrombin was then rapidly substituted for the tampon, and another piece of damp cotton placed on it. This, in turn,

was sucked dry. Even with active arterial bleeding, for example, during excavation of a meningioma, the second tampon could usually be removed within a minute, leaving the soluble cellulose solidly clotted.

This technic has been used in 30 operations of various types, with great satisfaction. In five instances, it appeared to be more effective than muscle. One of these was in a case of subfrontal meningioma, in which bleeding was a major problem. Another instance was in an operation of chordotomy in a patient with sarcomatosis, in which there was stubborn bleeding from peridural veins. The material saves much time in dealing with small oozing points on pacchionian granulations or from dural veins (Fig 1). It renders trigeminal root section a far easier procedure.

In most of these operations, the thrombin preparation made by Parke, Davis & Company, essentially by the method of Seegers, *et al*, was used. Lederle's "clotting globulin" and thrombin from human plasma, prepared by Cohn and Edsall,⁹ has also been employed with similar results. An accurate comparison between the various substances is impossible to make at present.

Obviously, other uses for similar preparations suggest themselves. Thin sheets of such treated cellulose might be used to control bleeding from the cut surface of parenchymatous organs, for example, the bed of the gallbladder. A similar gauze might be used in skin grafting. For first aid use in the field, an antiseptic such as sulfapyridine, penicillin or or gramicidin might be added to such tampons for packing deep wounds. Sulfapyridine has been added to the pledgets described above without affecting their hemostatic properties.

Appreciation is herewith expressed to the Lederle Laboratories, who supplied the clotting globulin, to Parke, Davis & Company, who supplied the Seegers' thrombin, and to Doctors Edwin Cohn, John Edsall and S. Howard Armstrong, who supplied the thrombin from human plasma. I am equally grateful to the Eastman Kodak Company which supplied the soluble cellulose. It was prepared by Mr. C. C. Unruh and Dr. W. O. Kenyon, and brought to my attention by Dr. Hans Clarke.

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CONVULSIONS DURING GENERAL ANESTHESIA^{*}

REPORT OF TWELVE CASES

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IT IS NOT OFTEN that there is justification for emphasizing a single symptom when considering the nature of a pathologic process but in the case of convulsions that occur during anesthesia there may be some excuse. A convulsion from whatever cause is always a dramatic event and when it occurs during an operation it is frequently the first and, indeed, may be the only recognized sign of what is believed to represent a serious and potentially fatal state.

The problem of convulsions during anesthesia has been largely the concern of the anesthetists, thus, the importance of discussing it before a surgical society may require some explanation. First, let it be said, that under any circumstances the surgeon cannot neglect his share of the responsibility for the safety of his patient, even though the anesthetist be an expert. Furthermore, it has become evident in the case of convulsions that there are probably many factors in the care of the patient before, during and even after operation that are as important as the anesthetic and which are largely the surgeon's responsibility.

The phenomenon in question is quite distinct from the familiar clonus or tremor seen during the induction of anesthesia, principally with ether, and it is not to be confused with the transitory muscular twitching that rather frequently is seen in later stages of the anesthesia, when oxygen intake is limited. The attack generally develops with twitching about the eyes and mouth when the patient is deeply under the anesthetic. There follow spasmodic contractions of the limbs and most of the muscles of the body, resulting in generalized and usually violent convulsive epileptiform movements.

As a basis for discussion of the subject a study has been made of 12 patients in whom convulsions occurred out of a total of about 75,000 subjected to general anesthesia during the past ten years at the New York Hospital. Excluded from the study are those instances in which convulsions developed after anesthesia and those occurring during "local" or nitrous oxide anesthesia. The latter group is omitted largely because the etiology of convulsions, postoperative encephalopathy and death with nitrous oxide anesthesia seems to be no longer a mystery but is almost universally accepted as due largely to anoxia of the brain¹. On the other hand this group is no doubt closely related to the cases to be discussed since anoxia in all prob-

^{*} Read before the New York Surgical Society, April 28, 1943

ability also plays the major rôle in convulsions during other forms of general anesthesia.

It is not so much, then, the convulsions themselves but the underlying state of which they are the manifestation that is of chief concern. That this is true is evidenced by the high mortality that accompanies the condition, it is too high to be accounted for by the occurrence of convulsions alone. It is variously estimated that the mortality is between 18 per cent² and 50 per cent³. The convulsions developing infrequently, as they do, and often without warning, have usually found the surgeon unacquainted with their importance and unprepared to deal with the problem intelligently.

The subject was introduced in England, in 1927, by the simultaneous reports of Wilson⁴ and Pinson⁵. Other reports of isolated cases followed in rapid order and, because all of the convulsions occurred during ether anesthesia, they came to be known as "ether convulsions." The inference was that the phenomenon was somehow related to the specific property of ether and, since but a few cases had been reported or could be recalled prior to that time,⁶⁻⁹ it was thought that some impurity existed in the ether which had not been present previously. The probability is that the condition existed before but went unrecognized, and we now know that convulsions and other cerebral complications occur not alone with ether but with other general anesthetics as well.^{1, 2, 10-18} In 1937, Lundy² reviewed the subject tabulated 144 cases largely from the literature, and listed a number of possible etiologic factors. A review in 1941, by Monroe and Benjamin,¹⁸ disclosed 168 cases reported.

Few seem to have had experience with more than one or several such cases, and too few details are presented in many of the reports. This has increased the difficulty of studying the nature of the convulsions and resulted in a multiplicity of ideas regarding their etiology. The conditions under which the convulsions occur are difficult to evaluate at best, and particularly difficult to duplicate in every detail for experimental study. Furthermore, there is a dearth of information from autopsy studies of such cases. A survey of the reported cases emphasizes the great variability in the circumstances under which the convulsions occur. In fact, the only apparent common denominator in all cases is an operation in which a general anesthetic is employed. Recent essayists on the subject have focused their attention largely on the single factor of anoxia in the production of which both the condition of the patient and the nature of the anesthetic agents play equally important rôles.¹⁹⁻²⁶

The following 12 case reports are of patients who developed convulsions during general anesthesia within the past ten years at the New York Hospital. Interest in the problem was aroused when one of us (Ray) observed the convulsions and postoperative sequelae to be reported in the first case. Through the assistance of the Department of Anesthesia it was arranged for one or both of us to be called to observe the convulsions that occurred in the other patients, or to appraise the circumstances soon

after the convulsions had occurred. Thus, it was possible to obtain fairly uniform and complete information about all the patients, from which certain deductions may now be made.

CASE REPORTS

Case 1—H F, female, age 36, was admitted, in April, 1933, with a subsiding acute cholecystitis. The past history was unremarkable. The patient was obese. Blood pressure 200/120, but EKG showed only left axis deviation. Blood urea nitrogen and routine laboratory tests were normal. After the acute episode had subsided, cholecystectomy and appendicectomy were performed. Preliminary medication of morphine 0.010 grams and atropine 0.0004 grams was given. Anesthesia was induced with ethylene and oxygen and maintained by the addition of 50 cc of ether vapor, using a closed mask. A "gallbladder bench" was elevated to improve the operative exposure. The patient's condition was satisfactory for 90 minutes, until the wound was being closed when, without any warning changes, twitchings began in the face. Rhythmic clonic movements appeared over the entire body, being more marked on the left side. Anesthesia was discontinued and closure completed. Oxygen was administered. Six hundred cubic centimeters of blood was removed by phlebotomy, which reduced the blood pressure from 185/98 to 115/80. Convulsions lasted 35 minutes. In the first six hours postoperatively four five-minute seizures occurred. Complete consciousness was not regained for 12 hours, and the patient remained restless and mentally sluggish for another 12 hours. A left hemiparesis was present and the patient complained of paresthesias on the left side. There was a sharp elevation in temperature the first two days. Rales were present in both lungs, and there was increased respiratory rate and dusky color for three days. There was 4+ albumin in the urine on the fourth day. The hemiparesis partially resolved, but eight years' follow-up reveals a residual weakness of the left lower extremity. An electro-encephalogram made eight years postoperatively showed "a borderline record probably normal."

COMMENT—It was believed at the time that the convulsions and subsequent hemiparesis were the result of a cerebral vascular accident but it is possible for focal signs to develop in the presence of generalized cerebral anoxia. Factors which may have contributed to the development of convulsions in this patient are cardiovascular disease and poor position on the operating table, resulting from elevation of the "gallbladder bench."

Case 2—J B, female, age 30, six weeks postpartum, was admitted, in June, 1936, with chronic cholecystitis and cholelithiasis. A past history of urticarial reactions to certain foods and dust was obtained. Physical examination and laboratory findings were normal. Phenobarbital 0.030 grams was given the night before operation. Preliminary medication of morphine 0.010 grams and atropine 0.0004 grams was given. Anesthesia was induced with nitrous oxide-oxygen. Maintenance was with ethylene, oxygen, and 65 cc of ether vapor, by closed mask. A "gallbladder bench" was elevated to improve the operative exposure. Cholecystectomy and choledochostomy were performed without technical difficulty. The patient's vital signs and general condition remained constantly good for 75 minutes, except that respirations were "jerky" and "irregular" at times. During closure of the wound generalized vigorous convulsions began rather abruptly. The anesthesia was stopped and closure completed. Oxygen was administered. Ten cubic centimeters of 10% calcium gluconate and 1 cc of parathormone were given, but no immediate effect of this was noted. Convulsions lasted 40 minutes. Four hours were required to regain consciousness but convalescence was

otherwise satisfactory During a five-year follow-up period no further neurologic disturbances developed An electro-encephalogram at the end of five years was normal

COMMENT—Factors which may have contributed to the development of convulsions in this patient are possible calcium and other nutritional deficiencies resulting from the recent pregnancy, plus the poor position on the operating table resulting from elevation of the "gallbladder bench"

Case 3—C K, male, age two, was admitted, in October, 1936, for repair of a cleft palate During the first year he had been treated for rickets but at admission he was found in good general condition Operation was postponed three days because of a rhinitis with low fever and a 24,000 leukocytosis After preliminary atropine 0.0008 grams, anesthesia was induced and maintained with ether, by the open mask method Later, ether was given by nasal catheter with a vaporizing machine Anesthesia was deep The pulse rate rose steadily from 120 to 180, and the respirations from 30 to 50 per minute Eighty minutes after the induction of anesthesia, generalized convulsions began and lasted 30 minutes Anesthesia was discontinued and oxygen administered Fifty units of parathormone and an infusion of 6% glucose in normal saline were given Temperature rose to 40°C Consciousness was regained in three hours, but the patient was unmanageable for an additional six hours Respirations were rapid for 36 hours and moist râles cleared gradually over the next three days Carbon dioxide combining power and total serum protein taken during the convulsions were 45 volumes per cent and 68 per cent, respectively On the first postoperative day serum calcium and phosphorus were 10.3 mg per 100 cc and 3.7 mg per 100 cc, respectively The recovery was otherwise uneventful, and the six-year follow-up has found no evidence of neurologic disorder

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are Youth, nutritional deficiency, recent respiratory infection, and relatively long and deep anesthesia

Case 4—M S, female, age six, was admitted with perforated appendicitis and purulent peritonitis in August, 1938 The past history was unremarkable The temperature was 39.6° C (rectal), pulse rate 140, and leukocytosis 28,500 Four hundred cubic centimeters of 5% glucose in normal saline infusion was given because of dehydration Preoperative medication was codeine 0.03 grams and atropine 0.0003 grams Anesthesia was induced with ethyl chloride and maintained with 90 cc of ether by open mask method Fifty minutes after induction, during closure, a generalized convulsion began and lasted several minutes Prior to this no noteworthy changes had occurred in the patient's general condition Anesthesia was discontinued Consciousness was regained in 90 minutes There was a rise of one degree of temperature over that recorded preoperatively, and the respirations were 40 per minute for the first 36 hours Thereafter recovery was uneventful Analysis of the ether found "no impurities" A four-year follow-up has found no other evidence of nervous disorder, except an electro-encephalogram done three years later showed "a borderline record, probably pathologic"

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are Youth, hyperpyrexia, toxemia; and dehydration

Case 5—T W, male, age six, was admitted in September, 1938, acutely ill with appendicitis of at least 30 hours' duration At the age of one he had had two generalized convulsions of unknown etiology which did not recur One month before

admission, he sustained a mild concussion of the brain from which he seemed to have recovered. Temperature was 38° C (rectal), and pulse 110. White blood cells were 21,000, but hemoglobin and red cell counts were normal. Preoperative medication was atropine 0.0002 grams. Anesthesia was induced and maintained with ether and oxygen through an open mask. Pulse rose from 100 to 160, and respirations were slightly irregular until 40 minutes after induction when facial twitching began. Generalized convulsions developed rapidly accompanied by irregular respirations and cyanosis. Oxygen was given and ether was reduced, but not discontinued, for 20 minutes to allow closure of the wound. The following medications were given—400 cc of 5% glucose in normal saline intravenously, 1 cc parathormone hypodermically, 10 cc 10% calcium gluconate intravenously, and, finally, after two hours and 20 minutes of almost continuous convulsions, 0.6 grams of sodium phenobarbital intravenously, which was followed by a diminution in intensity and then cessation of the convulsions for two hours. Temperature rose to 42° C (rectal) and pulse to 190. The urine contained 2+ albumin. Respirations remained rapid and the color slightly dusky. Consciousness was never regained and convulsions recurred intermittently. Frequently the seizures involved only the left arm. At first the deep reflexes were depressed but on the second day they were exaggerated and accompanied by bilateral extensor plantar responses. The spinal fluid contained 350 red blood cells and 0.075 Gm per 100 cc of total protein. The patient expired 40 hours postoperatively. No autopsy was performed. Analysis of the ether used showed impurities far below the U S P standards and essentially the same as in a control from a freshly opened can.

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are Youth, hyperpyrexia, toxemia, dehydration, and epileptic history.

Case 6—A H, female, age 40, was admitted, in August 1940, with an exacerbation of chronic cholecystitis. The patient had had frequent convulsions until the age of six, but none thereafter. Her son, age six, had convulsive seizures. Parenteral fluids were given but with the increase in clinical signs operation was decided upon. Temperature was 39° C, hemoglobin 10 Gm, RBC 3,400,000 and WBC 11,600. Preoperative medication of morphine 0.010 Gm and atropine 0.0004 Gm was given. Anesthesia was induced with nitrous oxide and oxygen and maintained by the addition of ether vapor (closed mask). A "gallbladder bench" was elevated to improve the operative exposure. Fifty-five minutes after induction of the anesthesia, convulsions began about the face and soon spread over the body. The respiratory rate had gradually increased to 35 per minute prior to the convulsions. Anesthesia was deep and only a little ether was needed for maintenance during the next 40 minutes required to complete the operation. Convulsions of about one minute's duration recurred every two to three minutes for 30 minutes. During the seizures the respirations were jerky and the color dusky but in the free intervals the signs became normal. Oxygen and carbon dioxide, separately or in combination had no appreciable effect but the condition improved shortly after the "gallbladder bench" was lowered. Recovery of consciousness was very slow, and for 36 hours the patient was irrational, incontinent, and had a temperature of 40° C (rectal). Three blood transfusions were given to improve the low blood pressure. There were periods of dyspnea and moist râles in the lungs for three days, a roentgenogram showed evidence of pulmonary congestion. After the third day recovery was steady. An immediate postoperative urinalysis showed 3+ albumin and a few erythrocytes, but later examinations were normal. Blood calcium and phosphorus were normal. Analysis of the ether used showed essentially no impurities. During two years' follow-up there was no recurrence of the seizures but a memory

defect and a personality change, characterized by emotional instability and hysterical outbursts, were evident

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this case are. Epileptic history, mildly toxic state, secondary anemia, and poor position on the operating table, resulting from elevation of the "gallbladder bench"

Case 7—L R, female, age 27, was admitted, in March, 1941, for menorrhagia caused by tubal pregnancy. Over the preceding two years she had had about ten attacks of syncope without convulsions, which were ascribed to hysteria since they were associated with fatigue and emotional stress. The carotid sinuses were not hypersensitive to pressure. Diagnostic dilatation and curettage of the uterus was done under nitrous oxide, oxygen and ether vapor, by the closed mask method. Morphine and atropine had been given preoperatively. The anesthesia lasted 45 minutes and was uncomplicated. Two days later a tubal pregnancy was removed. Morphine 0.010 Gm and atropine 0.004 Gm were given before operation. The anesthesia was the same as before and given by the same anesthetist. Near the end of the 90 minutes' procedure, without warning, violent generalized convulsions began and lasted six minutes. The patient was returned to the horizontal from the Trendelenburg position and anesthesia promptly discontinued. Morphine 0.015 grams was given. Recovery of consciousness was delayed and there were signs of partial atelectasis of one lung which disappeared shortly with treatment. Recovery thereafter was uneventful. Electroencephalography on the fourteenth postoperative day showed waves of mixed frequency which probably represented a pathologic state.

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are. A history of syncopal attacks; recent operation, and poor position on the operating table resulting from lowering the head of the table (Trendelenburg position)

Case 8—S D, female, age 27, obese, was admitted, in August, 1941, with perforated appendicitis and purulent peritonitis. She had given birth to her third child 11 days before. Right lower quadrant pain had been present for eight days and generalized abdominal pain for 36 hours. Temperature was 39° C, pulse 120, respirations 26, hemoglobin 14.5 grams, hematocrite 46, and leukocyte count 26,000. Urine showed a trace of albumin and 2+ acetone. One thousand cubic centimeters of 5% glucose in normal saline was given intravenously before operation. Preoperative medication was morphine 0.010 Gm and atropine 0.0004 Gm. Anesthesia was easily induced with nitrous oxide and maintained by the addition of 75 cc of ether-vapor and oxygen, by closed mask. The patient was said to have considerable "ether tolerance." Blood pressure rose steadily from 130/80 to 160/98, the pulse from 120 to 135, but respirations remained about 30. Fifty minutes after induction, and 35 minutes after the incision, convulsions began in the chin and neck and soon spread generally. Cyanosis then appeared. The anesthesia was discontinued and 100% oxygen administered. One cubic centimeter of paraldehyde and 250 cc of citrated blood were given intravenously. The temperature rose to 42.4° C (rectal). Colonic irrigations of cool water were given. The convulsions lasted for 90 minutes, thereafter the patient's general condition became steadily worse and she died five hours after operation. No autopsy was performed. The following laboratory examinations were made during this time: Spinal fluid normal, blood culture sterile, blood sugar 123 mg %, blood urea nitrogen 11 mg %, carbon dioxide combining power 52 volumes%; serum chloride 600 mg per 100 cc, total serum protein 6.7%, Cholesterol 234 mg %.

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in the patient are Recent pregnancy, hyperpyrexia, toxemia, and obesity

Case 9—J G, female, age 36, was admitted to the hospital, in September, 1941, because of abdominal pain from an ovarian tumor (theca cell tumor) The physical examination was unremarkable but for obesity The preoperative medication was morphine 0.010 Gm and atropine 0.0004 Gm Anesthesia was induced and maintained with cyclopropane plus 25 cc of ether vapor A uterine dilatation and curettage was followed by celiotomy and oophorectomy Eighty minutes after induction of the anesthesia the respiratory and pulse rates increased Ten minutes later hyperthermia was evident by a hot dry skin and the axillary temperature was 41.2°C The anesthesia was discontinued, oxygen given, the operating table lowered to the horizontal from a rather high Trendelenburg position, and an intravenous infusion of saline started The blood pressure fell steadily Forty-five minutes after cessation of the anesthesia violent and generalized convulsions occurred and continued until death 12 minutes later Autopsy disclosed congestion of pial vessels of the brain, pulmonary congestion, atelectasis of one entire lung, congestion of the kidneys, and petechial hemorrhages in the myocardium, pericardium and pleura

COMMENT—This is the only patient in whom there was an acute rise in temperature preceding the convulsions Probably an unrecognized atelectasis was the most important factor in the development of the hyperthermia and the convulsions Other factors to be considered as possibly contributing to the complications are Obesity, and Trendelenburg position on the operating table

Case 10—H F, male, age 44, was admitted to the hospital, in June, 1942, with what was thought to be gallbladder disease A mass was present in the right upper quadrant of the abdomen The hemoglobin was ten grams and the red cell count, 3.5 million Urinalysis was normal Serum prothrombin was 100%, and fasting blood sugar 99 mg % The red cell count rose to 3.9 million after a 500 cc transfusion of citrated blood Preoperative medication of morphine 0.010 Gm and atropine 0.0004 Gm was given Anesthesia was induced with nitrous oxide and maintained by the addition of ether vapor, by the closed mask method A large vascular neoplasm was found in the liver and only exploration was done The blood pressure rose slowly from 110/65 to 130/75, and the pulse rate from 100 to 125 Anesthesia was deep During closure of the wound 80 minutes after induction, facial twitchings began and were followed by generalized convulsions which lasted ten minutes Anesthesia was discontinued and oxygen administered Recovery from anesthesia was slow and the patient was partly irrational for two days For five days a sharp febrile reaction was present and there was evidence of a right sided pneumonia with pleural effusion Postoperative urine examinations all showed the presence of albumin An electroencephalogram two weeks after operation showed "a borderline record, probably pathologic"

In December, 1942, a multiple posterior rhizotomy was done for relief of intractable pain The same type anesthesia was used as before, but without complications A subsequent autopsy disclosed a metastasizing hypernephroma

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are Secondary anemia, and too deep anesthesia

Case 11—R S, female, age 40, was admitted to the hospital, in October, 1941, with chronic cholecystitis and cholelithiasis. Physical examination and routine laboratory tests were essentially normal except for the blood pressure of 170/110, and roentgenologic evidence of gallbladder disease. Morphine 0.010 Gm and atropine 0.0004 Gm were given preoperatively. Anesthesia was induced with nitrous oxide and maintained with ether vapor, by the closed mask method. Cholecystectomy and choledochostomy were performed. A "gallbladder bench" was elevated to improve the operative exposure. After 70 minutes of uneventful anesthesia twitchings began in the face, followed by generalized convulsions which lasted 15 minutes. Anesthesia was discontinued, oxygen administered and the "gallbladder bench" lowered. Sodium phenobarbital 0.13 grams was given intramuscularly, and 50 cc of 50% glucose intravenously. The post-operative course was unremarkable except for a persistent one plus albuminuria. Four months later the patient had no neurologic findings except that an electroencephalogram showed a pathologic record.

COMMENT—Factors to be considered as possibly contributing to the development of convulsions in this patient are Hypertension, unreplaced fluid and blood loss during a major operation, and poor position on the operating table resulting from elevation of the "gallbladder bench."

Case 12—B S, male, age 28, was admitted to the hospital, in December, 1941, with obstructive jaundice resulting from a stricture of the common bile duct. A biliary fistula was surgically established, but soon after a celiotomy was necessary for intra-abdominal bleeding. In February, 1942, a jejunostomy was performed to facilitate feeding the patient. The final operation was performed in April, 1942. Although he had lost weight steadily, the blood picture was relatively normal, total serum protein was 6.4%, and the prothrombin level was 94%. Jaundice had disappeared. Preoperative medication of morphine 0.010 grams and atropine 0.0004 grams was given. Anesthesia was induced with nitrous oxide and maintained by ether vapor (closed mask). The "gallbladder bench" was elevated. An anastomosis of the biliary fistula to the duodenum was carried out. Eighty minutes after induction of the anesthesia convulsions appeared in the face and neck, then spread to the entire body. For a half hour before, respirations had been irregular and faster and the pulse more rapid. The anesthesia was promptly discontinued. Ten cubic centimeters of calcium gluconate (10%) was given intravenously and a blood transfusion started. After 15 minutes the convulsions stopped and five minutes later ether anesthesia, by open mask, was resumed but convulsions returned, lasting for five minutes. Anesthesia was discontinued for the next 80 minutes while the operation proceeded. During this period sodium phenobarbital 0.13 grams was given intramuscularly. Cyclopropane was given for the last 40 minutes of the operation when the patient became restless, no further convulsions occurred. Recovery of consciousness required four hours, and for the next 18 hours the patient was restless, confused, and incontinent. After the first postoperative day there were no untoward developments. Electroencephalography 12 months later showed a normal record.

COMMENT—This patient was a relatively poor surgical risk though an effort had been made to improve his state prior to operation. This is the only case of the series in which operation was continued for any length of time or anesthesia of any degree resumed after the convulsions. It is noteworthy that on the first attempt to resume anesthesia, convulsions promptly returned. Probably the blood transfusion, phenobarbital and long period without anesthesia (80 minutes) served to protect the patient when anesthesia was finally resumed. The rather desperate circumstances in this

case perhaps justified continuing the operation after the convulsions had occurred, but in most cases such a policy can hardly be justified. Thus, the factors to be considered as possibly contributing to the development of convulsions in this case are: Three recent operations, biliary fistula, nutritional deficiency, unreplaced fluid and blood loss during a major operation, and poor position on the operating table resulting from elevation of the "gall-bladder bench."

ANALYSIS AND EVALUATION OF THE OBSERVATIONS IN TWELVE PATIENTS

Age and Sex—The ages of the patients varied from two to 44 years. Three were children under seven years, and the rest were 27 years, or over. One-third were males. Reviews on the subject^{2, 3, 27} indicate that the incidence is higher in females,²⁸ and that while children and young adults both are affected, the incidence is predominantly in children.²⁹ With the latter our figures are not in accord, yet the ratio of children and adults coming to operation during the period of our study is representative of a cross-section of the populace. The fact remains, however, that people past the age of 50, whose basal metabolic requirements are less than those of younger people, are nearly wholly immune to convulsions during anesthesia, and it may be inferred that vascular changes, general or cerebral, occurring after middle life do not predispose to this form of operative complication.

Seasonal Variation—One case occurred in March, two in April, two in June, three in August, two in September, and two in October. Some authors have emphasized that the convulsions have occurred during the hot summer months more frequently than at other times of the year. All of our patients were operated upon in air-conditioned rooms where constant temperature and humidity were maintained. It is suggested, therefore, that the season itself has little to do with the incidence of the convulsions, though the temperature of the operating room may be a different matter. Anesthetized persons tend to become poikilothermic and may easily become overheated in a poorly conditioned room.

Previous Convulsions—Two of the adults had had convulsions in early childhood, and one was given to syncopal attacks under conditions of fatigue. Although some authors⁹ have suspected that a predisposition to convulsions might be important as a factor in their occurrence during anesthesia, on the whole, the evidence has been unimpressive. It has often been observed that epileptics are likely to develop their convulsions during the inductions of general anesthesia or under light anesthesia,³⁰ but this is not to be confused with the subject under discussion. It appears paradoxical that general anesthesia, which is sometimes resorted to in the control of status epilepticus, should be responsible for convulsions in the nonepileptic.

Primary Disease and Operation—The diagnosis in three patients was appendicitis with peritonitis, appendectomy and drainage were performed in each. In two patients the diagnosis was chronic cholecystitis, and in one

acute cholecystitis; cholecystectomy was performed in each. In two patients there was disease of the common bile duct requiring tedious exploratory operation, with choledochostomy in one and repair of a stricture in the other. Two patients required pelvic operations, one for tubal pregnancy, the other for an ovarian cyst, and each had had preceding uterine curettage. One patient was explored abdominally for an hypernephroma with extensive metastasis to the liver. One patient, an infant of two years, underwent a long operation and difficult anesthesia for repair of a cleft palate.

Preoperative Condition of the Patient—With regard to the condition of the patients prior to operation, hyperpyrexia which exacts an increased demand for oxygen upon all tissues of the body is of the greatest importance.³¹ Payne²⁷ found that up to 1936, in 90 per cent of the reported cases the patients developed convulsions while being operated upon for "pyrexia disease." In our series, four of the 12 patients were acutely ill with high fever when they came to operation and, in addition, one child had not made a complete recovery from a respiratory infection. Toxicity and septicemia go hand in hand with high fever and it is probably of little use to try to separate their effects as far as the production of convulsions is concerned. However, Rosenow and Tovell³² attributed the convulsions to a neurotoxin produced by a streptococcus which is present in amounts insufficient to cause convulsions except in the presence of general anesthesia. Dehydration and acid-base imbalance, other states which so frequently accompany febrile diseases, may contribute to the initiation of convulsions by inhibiting the cells of the brain in their ability to utilize oxygen.³³⁻³⁵ Significance may be attached to the fact that many of the factors which have been thought to account for convulsions during anesthesia cause an increase in the H-ion concentration of blood and tissues.²¹

Deficiency in the nutritional state was present in at least three of our patients, two having recently gone through pregnancy, and one having lost considerable weight from the presence of a complete biliary fistula. Two patients had secondary anemia which increased the danger of anoxia during the anesthesia. In the first two patients, one of whom had peritonitis, an imbalance in calcium metabolism is to be considered as of possible importance. The effect of a low serum calcium in the production of convulsions is well known and several investigators have reported a depression in the serum calcium not only during anesthesia^{36, 37} but also in acute abdominal infections.³⁸ Alkalosis which may result from preoperative vomiting or by overventilation during the anesthesia is also capable of disturbing the calcium balance of the blood.³⁹

Position on the Operating Table—With regard to the hazards imposed by the operative procedure itself we feel that too little attention has been paid this possibility. It can be postulated that heavy retraction of abdominal wound edges, trauma,⁴⁰ excessive exposure of viscera to cooling, loss of blood, and other circumstances that are ordinarily associated with shock and "stagnant anoxia," may be said to be conducive, as well, to the develop-

ment of convulsions. But we refer more particularly to the position of the patient on the operating table. In five of the patients the back was acutely angled by the elevation of a "gallbladder bench." Two others were placed in high Trendelenburg position to improve the exposure in the operative field. These positions mechanically impede respiratory exchange and retard circulation.²² In one patient convulsions ceased dramatically with the lowering of a "high gallbladder bench" which had been overlooked during the distressing period when several other agents were being tried unsuccessfully in the control of the convulsions.

Preoperative Medication—The medication used in all patients of this series was limited to a standard dose of atropine with the addition, in adults, of 10 mg of morphine sulfate administered hypodermically 30 to 40 minutes before induction of the anesthesia. Barbiturates were not given to any of the patients preoperatively. Atropine has been implicated particularly by British anesthetists,^{41, 42} and others have emphasized the danger of anoxia, particularly of the histotoxic type, with the use of moderate to large doses of morphine and barbiturate derivatives.⁴³ While the possible rôle of these factors is undoubtedly too little recognized they are not considered to have played any part in the production of convulsions in the patients of this series.

Anesthetic Agents—The types of anesthesia employed in the cases reported were "Open mask" ether in three (namely in the three children), "closed mask" ether vapor with nitrous oxide and oxygen in six cases, ethylene (with a small amount of ether vapor) in two, and cyclopropane (with a small amount of ether vapor) in one. The percentage of nitrous oxide used with ether vapor anesthetics and of ether vapor with the ethylene and cyclopropane anesthetics was relatively so little that for the sake of brevity it may be said that the anesthetic agents in this series were ether by closed and open mask, ethylene and cyclopropane. Thus, there is support for the belief that the cause of the convulsions cannot be laid to one anesthetic agent^{1, 2, 10-18} or, in the case of ether, to the method by which it is administered. It may well be, as Courville²³ has suggested, that there is a certain "selectivity" by which different anesthetic agents produce their anoxic effects but the fact remains that any of the agents are capable of producing anoxia. It is to be emphasized that each patient was under deep anesthesia, perhaps several were too deep, but all were thought to be in no danger up to or near the time convulsions appeared.

Idiosyncrasy—The possibility that some patients have an idiosyncrasy to the anesthetic agent is difficult to evaluate but some⁴⁴⁻⁴⁶ have thought that such a state might exist, particularly with ether. Sears⁴⁷ and Kemp⁴⁸ reported instances of patients having convulsions during two different operations in which ether was used. In our series one patient had an uneventful 45-minute anesthetic two days prior to the operation during which she developed convulsions, and ether vapor, by the closed method, was used both times. Another patient had a longer and more difficult operation without convul-

sions six months after the one in which convulsions occurred, and again ether vapor, by the closed method, was used both times. These experiences, and others,⁴⁹ tend to refute arguments in favor of individual idiosyncrasy or allergy to ether.

Impurities in Ether —With the earlier cases we were concerned, as others have been^{46, 50-53} with the possibility of impurities in the ether, particularly since the ether was taken from drums. An analysis was made of the ether used in three of the cases*. The analysis in each showed .acetic acid eight parts per million, aldehyde and peroxide less than one-half per million. Tests made of control specimens of ether taken from freshly opened small cans and drums of ether showed the same values and these are far below the U S P levels for impurities. No other patients given ether taken from the same drums developed convulsions. A study of 700 cases was made at the New York Hospital⁵⁴ in which it was concluded from anesthetic tests that ether does not deteriorate rapidly when open and there is no difference between the effects of fresh ether used from small cans labeled "for anesthesia" and U S. P ether taken from drums.

It is not our intent to imply that anesthesia plays no part in the production of convulsions but rather to emphasize that certain specific anesthetic agents cannot, to the exclusion of others, be pointed to as the offenders.

Time of the Convulsion —It appears significant that the time found to elapse between the induction of anesthesia and the appearance of convulsions was between 40 and 90 minutes, with an average of 70 minutes. This suggests that whatever elements combine to cause the convulsions, time is required for their effects to appear. The majority of the cases heretofore reported have been of patients with acute appendicitis and the convulsions have appeared at about the time of closure of the peritoneum. However, it is believed that this time relationship is a coincidence and not otherwise important unless it be assumed that sometimes the deepening of the anesthesia for closure of the peritoneum plays some rôle.

Warning Signs —In none of the patients was there any cyanosis observed prior to the onset of convulsions and in four there were no untoward signs of any kind. In two there were respiratory changes only, such as "labored," "jerky," "increased" breathing. In four there was, in addition to respiratory changes, a significant increase in cardiac rate. In only two were there impressive changes in respiration, increase in cardiac rate and rise in blood pressure. The changes noted usually occurred gradually over a period of 20 to 30 minutes but in other instances they developed within 5 to 10 minutes prior to the convulsions. The appearance of cyanosis is too often relied upon as the early sign of insufficient oxygenation during anesthesia though it has been amply stressed in anesthesiology that cyanosis is neither criterion nor index of degree of anoxia. Lunsgaard and Van Slyke⁵⁵ have

* The analyses were made by Dr. Harry Gold of the Department of Pharmacology, Cornell University Medical College.

shown that cyanosis depends on the presence of a definite quantity of reduced hemoglobin in the blood and not upon relative proportions of reduced and oxygenated blood. Subclinical anoxia can exist without cyanosis and yet be of a degree that would be serious, if prolonged. More significant of developing anoxia is an increase in rate and amplitude of respiration, combined with gradual rise in blood pressure and cardiac rate with variation in the volume of the pulse beats²⁴

Temperature Increase—Only one of the patients gave evidence prior to the onset of convulsions of developing an increase in body temperature and in this patient nearly an hour passed between the appearance of hyperthermia and convulsions. Eight other patients had fever of 40° C, or more, some time after convulsions developed but three had little or no elevation of temperature at any time. There can be little doubt that under the conditions of increased body temperature, whether it be due to fever, overdose of atropine or external heat, patients, and especially children, are more prone to develop convulsions²¹. It is also true that convulsions of themselves cause an increase in body temperature. Some authors have held that an increase in body temperature was almost a prerequisite to the development of convulsions during anesthesia⁵⁶⁻⁵⁸ but in our series one-half of the patients gave no evidence of increased body temperature, at least until some time after the seizure.

Duration of Convulsions—The convulsions in all cases followed the same pattern, beginning in the face and spreading to the entire body. Single continuous convulsions lasted for periods varying from a few minutes to 90 minutes. In some patients there were recurring attacks over a period of hours, the longest period being 40 hours. In general, it may be said that the longer the single attack lasts or the longer the period of recurring attacks, the less chance that the patient will recover.

Mortality and Autopsy Findings—Death occurred in three patients, making a mortality rate for the series of 25 per cent. Autopsy was performed on one of these three (Case 9), and as far as the routine examination of the brain is concerned, no notable changes were found except a moderate degree of congestion as evidenced by dilatation of the small pial vessels. More impressive changes were disclosed in other organs, such as acute pulmonary congestion and atelectasis of one entire lung, congestion in the kidneys, and petechial hemorrhages in the myocardium, pericardium and pleura. The pathology found is compatible with that described by Courville¹ in the patients dying from anoxia with nitrous oxide anesthesia. Unrecognized atelectasis must always be considered as the possible source of trouble when convulsions develop during the operation⁵⁹.

While it would support our belief that anoxia was responsible for the convulsions and death in this patient if more impressive pathology could be demonstrated in the brain, it is likely that death occurred before detectable changes had an opportunity to develop. Courville¹ states that "changes in the nerve cells or in interstitial tissues are not characteristic until 36 to 40

hours have elapsed, time sufficient for physicochemical changes incident to anoxemia to become evident histologically "

Morbidity—All the patients who did not die showed either delayed recovery from anesthesia or late sequelae or, both. Delayed recovery was characterized principally by slow return to consciousness, restlessness, irrationality, delirium, confusion, uncooperativeness, incontinence. One patient has what appears to be permanent changes in temperament and personality while another has a residual hemiparesis. In the case of hemiparesis, while it is likely that a cerebral vascular accident occurred, Behrend and Riggs²⁰ have emphasized that individual variations in the cerebral vasculature are often the cause of clinical symptoms being referred to one side, even in the presence of diffuse cerebral damage. A lumbar puncture is of little diagnostic value since convulsions alone are often the cause of transitory increased intracranial pressure and red blood cells in the cerebrospinal fluid.

Electro-encephalographic Changes—It has been especially illuminating to find that in four of the seven patients subjected to electro-encephalography at varying periods after their operations, there were pathologic changes recorded. It would be useful to know whether changes which may be found early after the convulsive episode would persist but our data does not supply this information. Also, it would be necessary always to take into consideration the possibility that patients may have had abnormal brain waves prior to the time of the operation.

Other Effects of Anoxia—The clinical evidence for damage to other organs of the body as a result of the anoxia, presumed to have caused the convulsions, is to be found in the high incidence of postoperative pulmonary complications (in seven of the ten patients who lived longer than a day after operation) and of albuminuria (in five of the ten).

Blood Studies—Various blood studies made soon and late after the occurrence of convulsions in a number of the patients failed to disclose any significant changes. But no blood oxygen determinations were made and it is highly desirable in order to establish the importance of anoxia that more studies be pursued comparable to those of McClure, *et al*⁴³ in which changes in the oxygen content, capacity and saturation of the arterial blood were evaluated under various conditions of anesthesia.

DISCUSSION

The stage has perhaps not yet been reached at which the evidence can be said undisputably always to point to anoxia as the state underlying the occurrence of convulsions during anesthesia, yet the bulk of the collected data points in this direction. Since the brain cells and particularly those of the cerebral cortex are more susceptible to anoxia than other tissues of the body it is easy to explain the early occurrence of convulsions.

Barcroft's⁶⁰ classification of the anoxemias, based on physiologic principles, is useful in attempting to understand the many factors that must be evaluated in clinical cases. In the *anemic type*, present in patients with lack

of, or inactivation of hemoglobin, the red blood cells do not carry a normal amount of oxygen, although oxygen tension in the blood may be normal. In the *stagnant type*, because of slowed circulation, the oxygen supplied to the tissues is reduced. In the *anoxic type*, oxygen tension in the blood is lowered so that there is actually less oxygen in solution and because of an associated lowering of carbon dioxide tension there is decrease in the rate

TABLE I

FACTORS INFLUENCING THE ANO₂IC STATE AND DEVELOPMENT OF CONVULSIONS DURING ANESTHESIA*Factors Pertaining to Individual Susceptibility*

Youth
Female sex
Convulsive diatheses

Factors Pertaining to the Anesthetic Agents

Probably moderate anoxia upon which the production of the anesthetic state depends
Too deep anesthesia
Combination of anesthetic agents
Impurities in the anesthetic agent
Impure oxygen
Overoxygenation
Too much or too little carbon dioxide
Imperfections in the anesthetic machine

Factors That Increase the Oxygen Requirement of the Body Tissues

Fever
Heavy blanketing of patient
Overheated operating room
Hot weather

Factors That Disturb Circulation of Blood

Cardiac disease
Vascular hyper- or hypotension
Cerebral vascular accident
Reduced blood volume
Hemorrhage

Factors That Disturb Respiratory Exchange

Obstruction to air passages
Faulty aeration of lungs
Deficient alveolar absorption
Poor position of patient on operating table
Obesity

Factors Affecting the Oxygen-Carrying Properties of the Blood

Anemia
Poisoning (as carbon monoxide)
Sulfonamide therapy

Factors Which Possibly Affect the Tissue Cells' Ability Specifically to Utilize Oxygen

Acid-base imbalance
Dehydration
Hypoglycemia
Calcium imbalance
Nutritional deficiencies
Sedatives, opiates, atropine
Neurotoxin

of dissociation of oxyhemoglobin, all resulting in less readily available oxygen for the tissues. This type of anoxia may result from reduced oxygen in inspired air, obstruction in the air passages, faulty aeration of the lungs (as in atelectasis of the lungs) deficient absorption of oxygen from the lungs (as in pneumonia) or inability of the blood to carry a sufficient quantity of oxygen (as in the presence of methemoglobin). To these, Peters and Van Slyke⁶¹ have added the *histotoxic type* in which the tissue cells of the body, due to toxins or drugs,⁴³ are less able to utilize the available oxygen

CONVULSIONS DURING ANESTHESIA

It seems useful, then, to enumerate the various possible clinical factors that may contribute to the anoxic state and to the development of convulsions during operations in which general anesthesia is employed (Table I).

The inadequacy of this or any classification is well appreciated, it does not purport to be entirely original or complete. The placing of some of the factors under one heading and not under others is in many instances arbitrary, furthermore, some of those mentioned may be of no importance. But some order may thus be lent to the confusion existing over the numerous etiologic factors and it may more easily be seen that while one factor alone may be insufficient cause for the development of anoxia, the effects of two or more may readily be combined under the varied conditions of disease, operation and general anesthesia.

TREATMENT

Convulsions during anesthesia are relatively rare and probably much less frequent than other less dramatic effects of anoxia. A discussion such as this serves principally to draw attention to the nature of the state and the possibilities for its prevention by employing adequate preventive measures both before and during the operation.

When convulsions do occur it is advisable to (1) discontinue the anesthetic, (2) terminate the operation as quickly as possible, (3) administer oxygen, (4) correct any unfavorable position on the operating table, (5) keep the airway open (bronchoscopic aspiration may be required in case of atelectasis), (6) give some form of soluble barbiturate intravenously to control the convulsions, such as sodium amytal, sodium phenobarbital, or pentothal sodium, (7) replace blood or fluid loss, and (8) allay hyperthermia by sponging the body or irrigating the rectum with cold water. An oxygen tent provides the dual service of cooling and supplying adequate oxygen. There may be advantage in administering hypertonic glucose solution intravenously, particularly to combat unrecognized hypoglycemia and intravenous calcium gluconate or intramuscular parathormone to correct calcium imbalance.

SUMMARY AND CONCLUSIONS

An analysis of 12 cases in which convulsions occurred during general anesthesia shows

- 1 Convulsions occur in about one in 6,000 patients subjected to general anesthesia

- 2 The mortality rate is 25 per cent—too high to be the result of convulsions alone.

- 3 The term "ether convulsions" is misleading since the convulsions may occur during other types of general anesthesia

- 4 Most of the alleged causes of the convulsions are not of a nature to be alone or directly responsible. But most of them bear some relationship

to the delivery, transportation and utilization of oxygen for tissue respiration, thus suggesting anoxia as the chief factor in precipitating the convulsions

5 Since the cells of the brain are more sensitive to anoxia, convulsions often appear before other signs but when convulsions do appear an advanced state of anoxia may already exist

6 The incidence of convulsions during anesthesia may be lowered by attention to the preparation of the patient for operation, to the proper administration of the anesthetic and to the contributing effects of the operation itself

7 When convulsions occur all measures should be directed toward correction of the causative factors and alleviation of the state of anoxia. Some form of barbiturate should be given intravenously to control the convulsions

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ACUTE POSTOPERATIVE NECROSIS OF THE LIVER*

AN EXPERIMENTAL STUDY

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REPORTS by the white^{1, 2} in 1935 and 1936, dealt with acute postoperative necrosis of the liver in dogs following ligation of the hepatic artery. At that time two general conclusions were drawn. First, that so-called "high temperature liver death syndrome" is a clinical entity characterized by rapid progressive development of high temperature, falling blood pressure, circulatory collapse, coma and death, with a temperature as high as 109° F (human) within 36 to 48 hours after operation; and, second, that the essential lesion in the liver is diffuse central necrosis of the liver lobules. This syndrome was first described by Heyd,³ in 1924, and has been known since that time as "acute liver death," "high temperature liver death," "acute liver insufficiency," and the "hepatorenal syndrome." Autopsies have shown diffuse focal necrosis in the liver but no other lesions competent to produce the severe symptoms and the rapid death. The liver shows passive congestion, softening, and diffuse disorganization of the liver cords, with widespread areas of focal necrosis. Boyce,⁴ and Boyce and McFetridge⁵ concluded that in most instances when the clinical course is typical, the postmortem findings are typical, *i e*, necrotic changes in the liver with or without similar changes in the convoluted tubules of the kidneys, depending upon how long the patient lived after operation.

Experimental ligation of the hepatic artery produced typical lesions in, and rapid death of healthy dogs^{1, 2} when adequate collateral circulations did not exist. However, from this fact it can not be argued that this is the mechanism which produces necrosis of the liver in human beings. It does seem reasonable, nevertheless, to believe that the lesion is related in some way to conditions affecting the hepatic artery. Necrosis of the liver sometimes follows operations on the stomach, pancreas and other abdominal viscera and is frequently present in death of thyroid crisis.⁶ It may be that there is some common factor which links together necrosis of the liver, biliary tract surgery, operations upon the stomach, pancreas and other abdominal viscera and thyroid crises.

The vasoconstrictor nerves of the hepatic artery are derived from branches of the celiac plexus, and in their course to the liver are closely related to the extrahepatic blood vessels and the bile ducts. Therefore, these nerves are directly in the field of operations upon the bile ducts.

* Presented before the joint meeting of the Philadelphia Academy of Surgery, and the New York Surgical Society in New York, February 10, 1943.

and the gallbladder, and during such operations are subjected to trauma. In his exhaustive work on the vasomotors of the liver, Opitz⁷ demonstrated (1911) almost complete interruption of blood flow through the hepatic artery following faradic stimulation of branches of the celiac plexus.

Experiments were undertaken to determine the effect upon the liver of mechanical stimulation of the branches of the celiac plexus. In healthy dogs these nerves were mauled, clamped, pinched and roughly sponged. The immediate gross effect on the liver was the same as followed ligation of the hepatic artery. The surface of the liver became irregular in color, blackish in spots, and in other areas a mosaic discoloration appeared. In these areas it appeared as though the liver lobules were outlined by small black lines. These livers were of normal healthy dogs. No syndrome developed and the postoperative courses were smooth.

It is an accepted fact that disease of the gallbladder and the bile ducts is accompanied by hepatitis, and that each successive exacerbation of the biliary tract disease adds to the lesions in the liver. This must result in progressive impairment of liver function, but the factors of safety are so great that a liver may give no clinical or laboratory evidence of severe damage. Under the normal stress of living, these livers may function in an adequate manner, but under the abnormal strain of an operation and anesthetic, the slim reserve may be exhausted.

In order to conduct experiments in a satisfactory study of the effects of operations upon the gallbladder and bile ducts, comparable to the results in human beings, the experimental animals must have impaired liver function or liver damage. This impairment must be chronic, of slow development, and of such a nature as to allow the animal to live in an apparently normal manner.

Rousselot and Thompson⁸ (1939), in a study on "Experimental Production of Congestive Splenomegaly," induced cirrhosis of the liver in normal dogs by injecting a saline suspension of silicon dioxide into the splenic vein. Cirrhosis of the liver developed only after enough silica had been given, and enough time had elapsed to allow development of the lesion in the liver. In this study, the technic used by Rousselot and Thompson was used.

Twelve normal, healthy, adult male cats were used in the experiments. At celiotomy, 25 to 50 cc of a sterile saline suspension of silicon dioxide* (one per cent) was injected slowly into the splenic vein. At intervals of six weeks a second and a third injection of the silicon dioxide suspension was made in the splenic vein of each cat. At the second operation, well developed gross silicosis of the hepatic regional lymph nodes was evident in each animal and at the third operation there was beginning gross evidence of cirrhosis of the liver. Nine cats died at various periods during

* Silicon dioxide suspension, one gram in 100 cc normal saline. The individual silicious particles are 1-3 micra in diameter.

The silica was prepared by Dr Leroy U Gardner, Director of the Saranac Laboratories, Saranac, N. Y.

POSTOPERATIVE NECROSIS OF LIVER

FIG 1

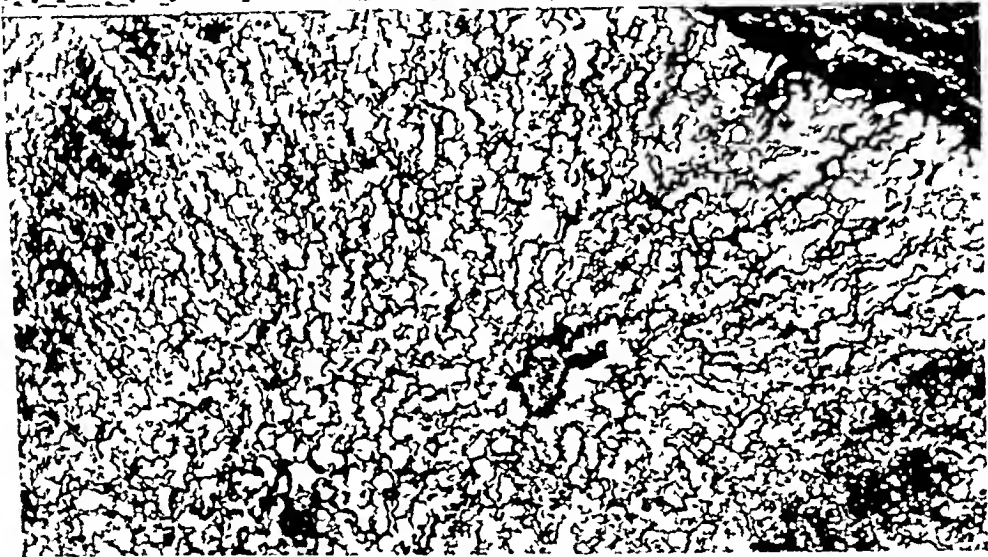


FIG 2

FIG 1—Normal liver, cat Trichlorsilver stain shows no intrahepatic connective tissue ($\times 225$)

FIG 2—Experimental cirrhosis of the liver, cat Connective tissue (black), demonstrated by trichlorsilver stain, is widespread, and encloses the cords of liver cells ($\times 225$)

the time necessary to induce cirrhosis of the liver, and sections of their livers showed cirrhosis in direct proportion to the degree of silicosis of the regional lymph nodes (Figs 1 and 2)

Three cats which received three injections of saline suspension of silicon dioxide, lived through the summer months, and appeared to be in good condition for the concluding experiment. At the operation, each cat showed gross cirrhosis of the liver with ascites. In each case a cholecystectomy, from cystic duct to fundus, was performed, and this was immediately followed by intermittent stimulation of the branches of the celiac plexus with faradic current from an induction coil, for two minutes. Each cat died promptly, in less than 18 hours after operation. Autopsies

showed congestion of the liver, and areas of softening. There was no hemorrhage, thrombosis or other cause of death. A clinical thermometer sewed in the abdominal cavity at the conclusion of the operation did not show any rise of temperature. Microscopic sections of these livers (Fig 3) show congestion and diffuse focal necrosis.

Three normal, healthy adult male cats were used as controls. The same procedure (cholecystectomy and faradic stimulation of branches of the celiac plexus for two minutes) was used. All of these animals survived for an indefinite period following the operation and nerve stimulation. A second operation was performed on one of the controls. At the first operation a small gauze sponge was left in the subhepatic region. At the



FIG 3—Liver of cat in which experimental cirrhosis was produced. Death followed faradic stimulation of branches of the celiac plexus ($\times 225$)

(A) Hematoxylin and eosin stain. Circular areas of liver necrosis (N)

(B) Trichloro-silver stain of the same liver. Note circular areas of necrotic cells (N), outlined by connective tissue

second operation the liver, stomach, bile ducts and intestines were involved in many dense adhesions. Separation of these adhesions to expose the bile ducts and the celiac plexus produced severe trauma. Faradic stimulation of the nerves for two minutes produced no effect, and the animal made an uneventful recovery.

The microscopic pictures of the livers of (1) human beings dying a "liver death," (2) dogs following ligation of the hepatic artery, and (3) cats with cirrhosis of the liver, which have died following cholecystectomy and intermittent faradic stimulation of the celiac plexus, are the same. They

show diffuse focal necrosis of the liver. It seems reasonable, therefore, to conclude that fundamental cause of the so-called "liver death" syndrome is a badly damaged liver. Stimulation of branches of the celiac plexus, during operations upon the gallbladder and bile ducts, produces spasm of the hepatic artery. This spasm deprives the liver of its arterial blood supply (Opitz⁷) and an irreversible reaction is initiated, which results in diffuse focal necrosis of the liver. It also seems reasonable to conclude that the essential pathologic lesion in the liver of human beings, dogs, and cats is the same—diffuse focal necrosis.

Local injections of novocain in the gastiohepatic omentum anterior to the foramen of Winslow or novocain block of the celiac plexus should prevent impulses traveling along these nerves to the liver. Although, in this study, no experimental nerve or plexus blocks have been performed, I believe that such measures should be used when one encounters a firm, irregular liver or gross evidence of cirrhosis, if biliary tract surgery is contemplated.

Grateful acknowledgment is made to Dr. Allen O. Whipple for the opportunity to undertake this work in his department, to Dr. Arthur Purdy Stout, for suggestions and examination of specimens, to Major Louis M. Rousselot, MRC, U. S. Army, for assistance and suggestions, and to Miss Daisy Mapes for assistance and care of the animals.

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BRIEF COMMUNICATIONS

MASSIVE FIBROMA OF THE SCALP

CASE REPORT

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THIS CASE IS presented because of the size and peculiar appearance of the tumor, and also because of the surgical problem involved

Case Report—G D, white, male, age 23, entered the Saskatoon City Hospital complaining of a growth covering a large portion of the right side of his head. The mass had been present since birth and had enlarged as he had grown. For the past several years it had remained practically stationary. He had been advised against operation, because of the danger of hemorrhage. He had been rejected for service in the army. We felt it was of great importance to the future of this young man if this mass could be removed successfully. It is self-evident that such a glaring deformity must give anyone an inferiority complex.

The general examination and history were irrelevant. Examination of the mass revealed a partly lobulated growth, 16 cm in length, 12 cm in width, while the



FIG 1—Lateral view of fibroma prior to operation



FIG 2—Anterior view of fibroma prior to operation

greatest thickness was almost 5 cm. The surface was smooth and hairless, but was indented quite deeply by characteristic sulci which, with the pale pinkish color, gave it the appearance of exposed cortex. The mass was very hard, though slightly movable, but was attached to the scalp completely to its actual periphery. The growth of normal scalp hair ended abruptly at the exact border of the tumor (Figs 1 and 2). Roentgenograms demonstrated no involvement of the skull.

Surgical Procedures—January 9, 1942. Biopsy was performed, and the sections were reported upon by Dr W S Lindsay, pathologist, University of Saskatchewan, as follows. **Pathologic Examination—Microscopic**. Section shows a thin but uniform and typical covering of stratified squamous epithelium. Beneath this is an interlacing mass

of dense strands of collagen with few fibrocytes. In many of these strands there is a vessel or slit lined by endothelium which is thickened and shows some activity, and masses of endothelial cells are found embedded in the fibrous strands (Fig 3) *Pathologic Diagnosis* Lymphangiofibroma — no evidence of malignancy Keloid

January 12, 1942 The scalp was infiltrated with 1% novocain solution. The removal of the tumor was commenced by electro-section at its posterior border. The very numerous vessels were coagulated at once. However, it was soon evident that the heat penetrated to the skull, though the usual precautions were used. The entire central mass of the tumor was, therefore, removed leaving a mat one centimeter in thickness and the rim of the tumor almost intact (Fig 4). The raw surface was dressed with vaselined gauze.

January 17, 1942 Again using local anesthesia, the entire floor of the tumor was removed, together with a considerable of the edge of the tumor. The border of the tumor was now raised and loosened. Because of its density, silk sutures could be inserted and drawn very tightly. This allowed us to displace the periphery of the tumor, so as to reduce the uncovered area (Fig 5).

February 5, 1942 Under general anesthesia, the previous tension sutures were removed and the remaining edge of the tumor excised. Hemorrhage was of considerable moment, many of the vessels being so large that ligation was necessary, as they could not be successfully occluded by coagulation.

The scalp was now loosened over the vertex, forward over the frontal region, and backward, freeing most of the occipital area. The neck tissues were undercut



FIG 3 —Pathologic section of fibroma showing fibrous tissue and vessels lined with endothelial tissue

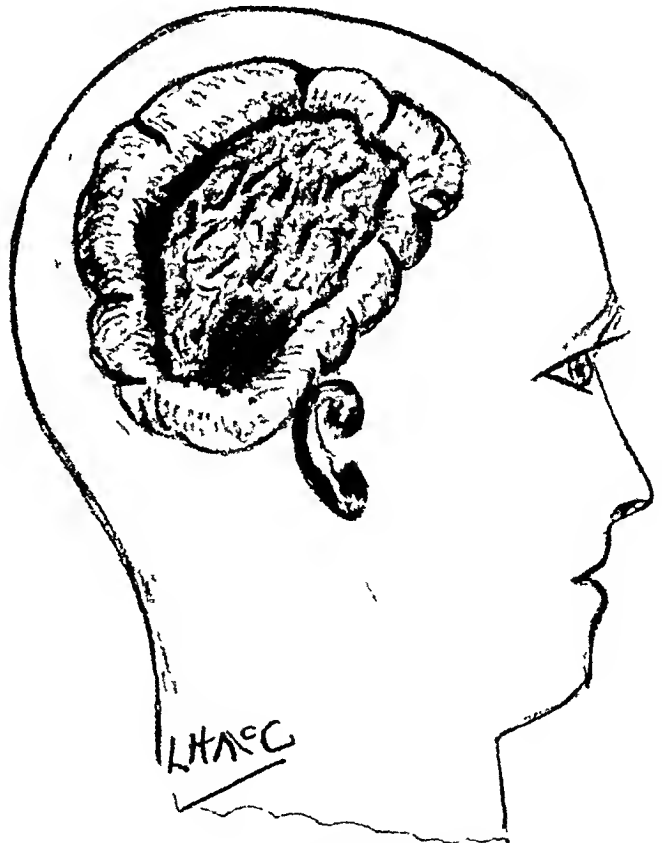


FIG 4 —Appearance after first operation

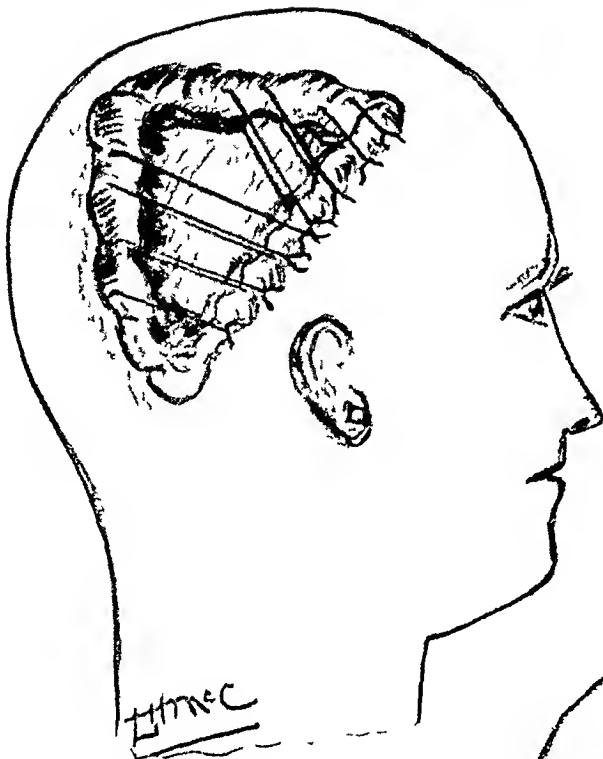


FIG 5—Following 2nd operation, showing tension sutures

behind the right mastoid. A linear incision was made in the mid-occipital region as well as a prolongation of each edge of the excised area downward and backwards behind the right mastoid.

The scalp was now stretched by strong traction and sutured (Fig 6). Happily, this patient had a fairly loose, pliable scalp. The full use of the above measure reduced the uncovered area to a triangular space 5×10 cm.

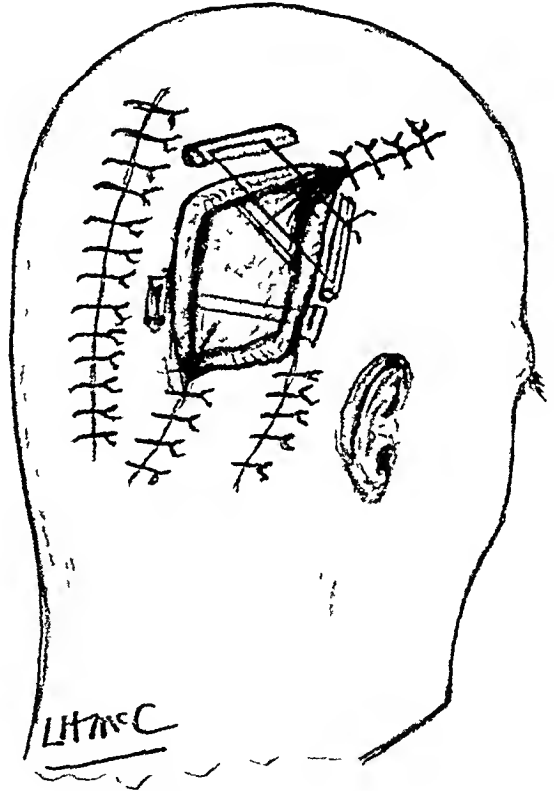


FIG 6—Following 3rd operation, showing incisions necessary for plastic attempt

Postoperative Course—The tension sutures were removed after two weeks, and the area grafted with foreskins removed at circumcisions. The mucous membrane being first removed, each specimen was sectioned conveniently into six pieces and applied and covered with a dressing of Ringer's solution. About two-thirds of the grafts were successful. The area was completely covered by March 30, 1942 (Fig 7). After his hair had regrown, he returned to show us the result. He is very grateful because of his changed appearance (Fig 8).



FIG 7—Appearance on discharge



FIG 8—Nine months following operation

SUMMARY

A large fibroma of the scalp, of unusual appearance, is reported, and the stages of its removal described. Photographs and drawings are presented illustrating the work done. Careful planning of each procedure is of the greatest importance.

A METHOD OF FIXATION FOR FRACTURES OF THE STERNUM*

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CANADA

FRACTURES OF THE STERNUM are comparatively rare. Those with displacement frequently cause serious disability. The most common site of injury is probably the junction of the manubrium with the body of the sternum.

The stooping posture of the patient is characteristic. Complaints of upper substernal pain associated with dyspnea are suggestive of such an injury. There may be deformity, but this is easily obscured by swelling,

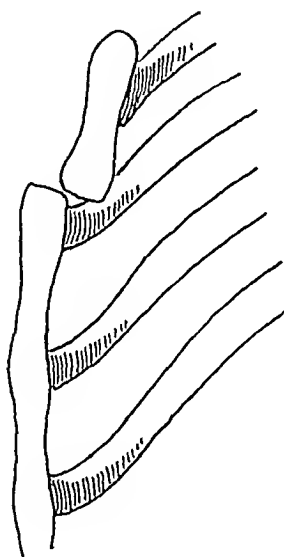


FIG 1—Sketch from roentgenogram (retouched) showing the fracture dislocation of the sternum, with backward displacement of the manubrium

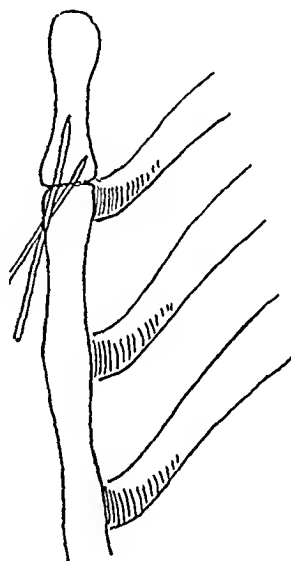


FIG 3—Sketch from post operative roentgenogram showing complete reduction, with the wires in place

while the natural variations in the prominence of that portion of the sternum render this sign of somewhat lesser importance. There is localized tenderness at the point of injury, but the tenderness is sometimes more widespread due to concomitant injuries to the sternochondral articulations.

Satisfactory roentgenograms are difficult to obtain, and the patient should not be subjected to too much movement for roentgenologic investigation until he has recovered from his initial shock, which is sometimes very considerable.

Rupture of the internal mammary artery has been reported as a complication¹. Spontaneous reduction is said to sometimes occur on coughing.

* Permission to publish this article has been granted by the Department of National Defense, Ottawa, Canada. Brigadier J. C. Meakins, Deputy Director-General of Medical Services.

or sneezing.² Some cases can be reduced by manipulation in the position of upper dorsal hyperextension, with the head and shoulders hanging over the edge of a table. Other cases require open operation and sometimes fixation to maintain reduction. Such a case is herewith reported.

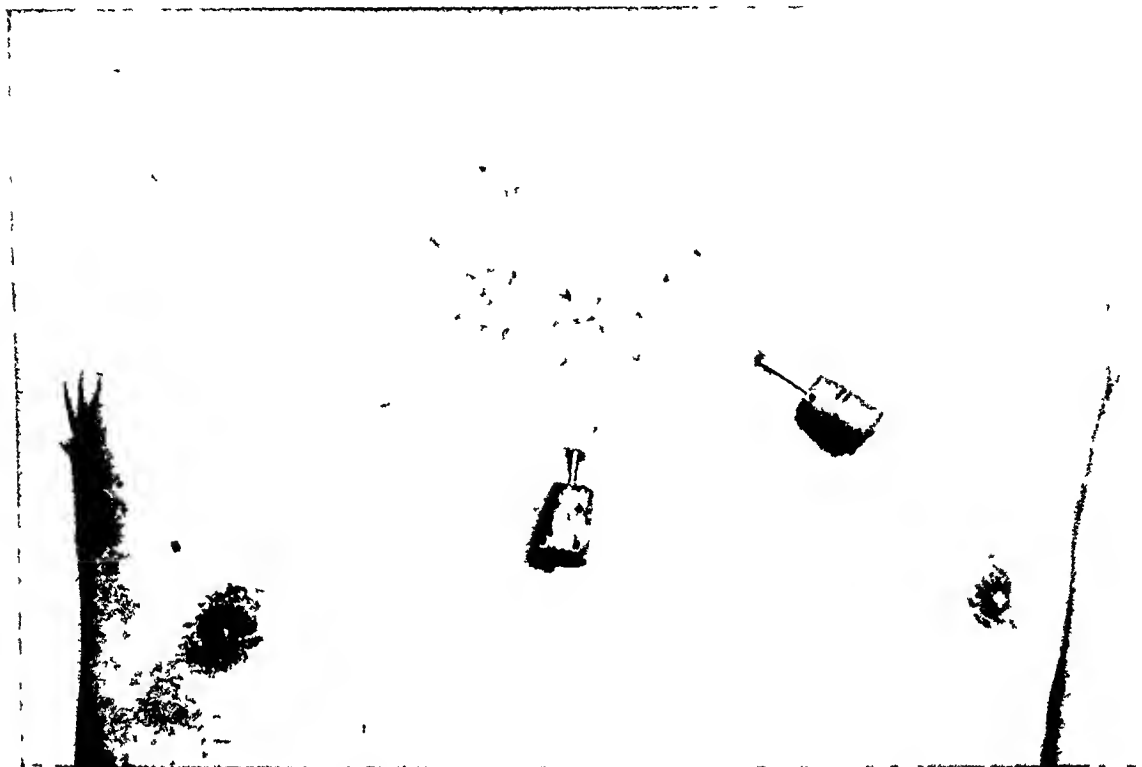


FIG 2—Photograph showing site of incision, and the management of the Kirschner wires

Case Report—Lieut J T was admitted, November 18, 1942, suffering from injuries received in a motorcycle accident. There was a history of a brief loss of consciousness.

Examination showed multiple lacerations and contusion of the face, scalp, right arm and anterior chest wall. He complained of pain on compression of the upper chest. These complaints were thought to be explainable by the multiple contusions present. There was a moderate degree of shock. Roentgenograms of the skull showed no fracture.

Six days later his thoracic pain became more localized in the region of the upper portion of the anterior chest wall. The other areas of contusion were no longer complained of but he felt a constant sense of substernal distress, with dyspnea, especially on movement. A definite area of tenderness at the manubriosternal junction could not be quite sharply localized. As he could now be moved without too much discomfort, more extensive roentgenologic examination was carried out, and it was possible to demonstrate a fracture-dislocation of the sternum, with backward displacement of the manubrium (Fig 1). Even with the knowledge so gained, the displacement could not be made out by palpation.

Attempts at reduction by hyperextension were unsuccessful, and open reduction was considered necessary. Operation was performed on November 27, 1942, nine days after injury, under local anesthesia. The fracture line was exposed by a short curved incision about one inch below the point of fracture. The depressed portion (manubrium) was elevated, but owing to a sloping fracture involving the posterior surface of the lower fragment, reduction could not be maintained and fixation was necessary. This was

accomplished by a Kirschner wire, which was inserted through a point about two inches below the incision in the skin and passed upwards through the body of the sternum to cross the fracture line and penetrate superficially into the manubrium

A second wire was passed transversely through the sternum and into the end of the second rib on the right side. This was made necessary by a complete detachment at the second chondrosternal articulation. The wires were allowed to project about three-quarters of an inch from the skin, and corks were applied to their ends (Fig 2). A postoperative roentgenogram showed complete reduction, with the wires in place (Fig 3). The skin wound healed *per primam*. The wires were removed December 24, 1942, four weeks after insertion, and the patient was permitted to leave the Hospital for sick furlough four days later. The complete and permanent relief of all symptoms from the moment of reduction was quite spectacular.

To the best of my knowledge, this method of fixation has not previously been reported. While it is probable that many cases requiring open reduction need no fixation, the simplicity and effectiveness of this method, when necessary, is considered sufficient excuse for its publication.

SUMMARY

A case of fracture of the sternum with posterior displacement of the manubrium is reported.

A simple and effective method of fixation after reduction is described.

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- ² Magnuson. Fractures. 4th Edit. J B Lippincott Co, Philadelphia, 1942.

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MEETING HELD AT CINCINNATI, OHIO
MAY 13-14, 1943

ADDRESS OF THE PRESIDENT THE IMPORTANCE OF FUNDAMENTALS IN SURGICAL EDUCATION^{*}

VERNON C DAVID, M D
CHICAGO, ILL

MAY I sincerely thank you for the honor of acting as your presiding officer at this meeting. It is an office both unsolicited and unexpected but one which will ever remain a high light in the professional life of the recipient.

The subject of my address to you is influenced, as, indeed, are most of our thoughts and plans these days, by our active participation in the war. Our whole social structure is profoundly affected and is being remoulded to allow us more adequately and effectively to do our part. One aspect we feel is the impact of war on medical education and particularly on graduate education, and, with your indulgence, I shall consider some of its effects and consequences on surgical education and point out what seem to me important principles to maintain in our post-war medical educational program.

No such discussion is of the slightest value unless we win the war, and to that object the medical men of the allied countries are giving all of their energy and talents. The tradition of service has always been fundamental in the practice of medicine but is never more in evidence than in time of war. The responsibilities of family, teaching, and practice are overnight transferred to active service by those whose youth and virility permit, while the older and less active attempt to become younger and more active in all useful duties on the home front. Medical men of the United States and Canada have reason to be proud of their participation in the wars of their

^{*} Presented before the American Surgical Association, Cincinnati, Ohio, May 13-14, 1943.

countries, and the essential necessity and quality of their services have always been recognized. We have come a long way from the beginnings of our medical service in war when, in 1775, the Provincial Congress in anticipation of war, and as one of its first acts of preparation for war, authorized the purchase of fifteen surgeons' chests, hoping to have one assigned to each regiment. At the time of the Revolutionary War there were but two medical schools in the United States (Philadelphia, 1765, New York, 1760) both of which closed during the war and, up to that time, less than fifty medical degrees had been given by them. There were, however, a number of Scotch and English doctors (among them Hugh Mercer, James Craig, and St. Clair) who had settled in America and who volunteered for service, although most of them accepted commissions in the line. To bear evidence of the quality of the medical men of those days, we are proud to remember that six doctors signed the Declaration of Independence, six became Brigadiers and several Major Generals. The First Provincial Congress of Massachusetts had twenty-two medical men as members, two of the outstanding being Joseph Warren and Benjamin Church.

The participation of medical men of the United States in the First World War is still fresh in the memories of many of us. There were 31,501 of them commissioned officers. Dr. George Brewer, in his presidential address, in 1920, recounted the services of this Association. One hundred and seven of our members held commissions in our own or allied armies. Fifty-seven served in France, 22 were decorated for meritorious service, ten received citations, and 47 served in front areas during one or more great battles.

It will, therefore, be of little surprise that about 47,000 doctors have accepted commissions in this war. From our own society fifty are commissioned officers, and many others are serving in an advisory capacity. The complete record must be left to a later and more complete summary.

The effect of war on medical education is the tendency to lower standards in the preliminary education of medical students, to accelerate their medical instruction, and to greatly reduce graduate education. All of these factors hold the threat of lowering the quality of medical education which, in turn, limits the effectiveness of the medical man both in war and peace. While perhaps in a degree necessary because of war, the threatened curtailment of premedical education strikes at the very foundations of education for, in order for the physician of the present or future to take his proper place in our social structure, he must not only write plainly and read understandingly but he must have some knowledge of what has happened to the world in the past in order to help build soundly for the future. Doctors today play an important rôle in prescribing for society and its institutions as they relate to public health as well as to care for bodily ills.

The accelerated medical curriculum leaves no time for the student to interest himself in other than routine work, and the short period of internship and greatly curtailed resident system obviate to a large degree training

and investigation carried out in the scientific laboratories. Our middle-aged group of surgeons who have attained their graduate training have been promptly and properly inducted into the Army and Navy, with a consequent disorganization of many of our hospitals, teaching, and dispensary staffs that leaves the older ones of us in the saddle doing our best to carry on with the determination to maintain our medical instruction at the highest level possible, and to prosecute investigation in problems arising in war medicine. The most serious results to medical education lie in the curtailment of a sufficient period of graduate training and especially as it relates to continuation of training in the fundamental science branches as applied to surgical problems.

If the war lasts several years, there will go out into military service 10,000 to 20,000 young medical men who have had no other graduate training than one year of internship. Canada's effort to recall from military service some of the most promising young medical men to teaching hospitals for a year of resident training, as a reward for meritorious service, is a worthy one and is now being considered by our Navy. This would not only serve as a reward for outstanding service but would render a picked group further education which would be of signal service to the Army and Navy but would insure to post-war medicine a needed lift in quality.

On the assets side of the war ledger are many human values as well as some educational ones. In addition to the pride of service during war, our young medical men in war will soon develop a sense of organization underlying conditions, will become more self-reliant, will develop the power of quick decision, and will place a high value on the simple fundamentals of life as loyalty, self-sacrifice and team work, which go far to develop a sound viewpoint which from now on will be of necessity a world viewpoint. Never before have circumstances and inclination combined more effectively to solidify our North American ideals, policies, and scientific objectives.

With the war won, and our medical men returned to peace time activities, we will be faced with many difficult problems for solution of which I shall only consider the continuation of graduate training. The mental unrest following sustained war effort, the change of pace and objective in the day's work, the necessity of reestablishment of home and sustenance, the changed emphasis on the values of life will make for temporary disorganization in the lives of our returning medical men, but we should not forget it is to that group that we must look for the medical leadership in the post-war days. The outstanding men in surgery during the past twenty years were practically all men who had risen to their responsibilities in war service in the First World War. We must see to it that for a similar group returning from this war important posts are made available in our medical schools and hospitals and that they are made to feel our confidence in their ability to reestablish and maintain high medical educational standards. A very large group of men having had one year of internship will go to war without resident training. Some of these men will continue active professional work in Army or Navy.

assignments but many will return to civil life with more worldly but little medical experience. It is to be hoped that from this group many can be chosen for resident training or be given assignments in the fundamental science laboratories so that their war age-group may be given the educational advantages which provide the creative and imaginative mind with the necessary tools for advancement of our knowledge in medicine.

The selection of such a group for further training will test our most mature judgment, for the factors of their experience and ability in war surgery must be weighed in the balance with available facilities and the proper number of carefully trained specialists deemed essential in our medico-social structure. Above all, training of specialists requires, more than ever before, thorough grounding in the basic sciences.

It may not be without interest to briefly trace the importance of fundamental science training in the development of surgery as a specialty. While surgery has been practiced from the earliest times, as we know from the description of trephining and splinting in the 17th Century B.C. Smith Papyrus (which itself was a copy of an ancient Egyptian manuscript), the main incentive to the development of surgery was the care of war casualties. Hospitals appeared from 1100 to 1700, and there was an increasing tendency to train surgeons in them. The history of St. Bart's Hospital, London, founded in 1123, gives an impressive procession of such events. A certain amount of surgical specialism developed in bloodletting, treatment of fistula by John Arden (1306-90), and cutting for stone by Cheselden (1688-1752). It was as late as 1731, however, that the Royal Academy of Surgery of Paris was founded, which was entirely devoted to surgery and, in 1745, that the surgeons of England split entirely from the Barbers' Guild.

Scientific surgery was brought to London by William and John Hunter. Before their time surgery was an art dealing with individuals, as the late Sir Darcy Powers so aptly said. William Hunter gave his first course of anatomy in 1746, and founded the Great Windmill Street School of Anatomists. Numbering among its pupils were Hewson, Sheldon, Cruikshank, and Ballie, and resulting from its work were definite advances in our knowledge of the circulatory and lymphatic systems. Its teachings produced surgeons of the caliber of Abernethy, Astley Cooper, and John Hunter, of London; Hey, of Leeds; and our own Philip Syng Physick, of Philadelphia. John Hunter and his pupils took a wide view of surgery, and in their studies explored the architecture of the bodies of animals as well as man, and founded a school of surgery that was devoted to investigation and advancement of knowledge mainly through anatomic and pathologic channels, for at that time chemistry was in its infancy and physics was first beginning as a science, and the compound microscope was not in use.

In the Royal College of Surgeons in Edinburgh is now housed the collection of anatomic dissections of Sir Charles Bell. His interest and investigations in the anatomy of the nervous system, carried on for fifteen years in the Great Windmill Street School, resulted in the description of both

the external respiratory nerve and peripheral seventh nerve palsy in 1821. Later his "Anatomy of the Brain" gave an entirely new concept to the physiology of nervous tissue.

In France and Germany continuing wars were a hindrance to the development of scientific surgery but developed great technical surgeons, as Dupuytren, Larrey, and Bardeleben. Working as an assistant to Dupuytren was a young man who observed with interest and curiosity that the application of Dupuytren's spur-crushing clamp applied to the open end of opposing loops of bowel did not cut through the bowel to cause peritonitis. He pondered on what caused the opening surfaces of the bowel to agglutinate. As a result of many experiments on animals, Lembert described, in 1826, the agglutination of opposing peritoneal surfaces by fibrin, and devised the Lembert suture, which principle has made gastro-intestinal surgery possible.

Largely as a result of the inspiration and training acquired in these first beginnings of scientific surgery in London, Edinburgh and France, Morgan, Shippen and Rush founded the first medical school in this country in Philadelphia in 1765. The Warrens became the leaders of surgery in Massachusetts, founded Harvard Medical School in 1783 and the Massachusetts General Hospital in 1811, which later, in 1846, in Warrens' Clinic, became the setting for the first public demonstration of ether anesthesia. McDowell returned from Edinburgh to Kentucky to perform the first ovariectomy in 1809.

Samuel D. Gross, a founder and first president of this Association, published, in 1828, a translation of Boyle and Hollard's "Manual of General Anatomy" followed, in 1830, by a book of his own, "The Anatomy and Physiology and Diseases of Bones and Joints," which he said was "to discharge in part that debt which, according to Lord Bacon, every man owes to his profession."

The development of the science of physics gave great impetus to the development of eye surgery when, in about 1831, von Helmholtz invented the ophthalmoscope. A young group of well trained general surgeons, by their scientific attainments, placed ophthalmic surgery on a high level. Argyl Robinson, who became the great eye surgeon of his time, was first a house surgeon and later taught physiology.

Surgical pathology made great progress after the development of the compound microscope, from 1812 to 1830, and schools of thought developed around Virchow and, later, Cohnheim in Germany, Billroth, in Vienna, and Sir James Paget, in England. Students were attracted from many parts of the world and they, in turn, spread the gospel of sound pathological training as fundamental to good practice of medicine.

As late as 1864 the causes of fermentation, putrefaction, and suppuration in wounds was unknown, and in that year Pasteur exploded the theory of spontaneous generation as a cause of putrefaction. This fundamental work almost immediately attracted the attention of Joseph Lister, whose early education may be of some interest in emphasizing the importance of training in the basic sciences in preparing the creative clinician.

Joseph Lister (born in 1827) had an illustrious father, a merchant by occupation, but with many scientific interests. He was especially concerned with the development of the achromatic lens of the microscope. In his medical education Lister early came under the guidance of Sharpey in physiology and, later, Nolan in chemistry, both of whom had a great influence in his understanding of wound healing. He then had a sound course of clinical instruction under James Syme, Professor of Surgery at Edinburgh. His earliest papers in Edinburgh were on duration of vitality in tissue, early stages of inflammation, gangrene, coagulation of the blood, the function and structure of nerves regulating contraction of arteries—all basic studies which reflected the breadth of his thought and training. In Glasgow he had a large service in traumatic surgery and became intimately acquainted with the consequences of infection and the enormous mortality following wounds or surgical operations. A most natural reaction was his interest in, and study of, the distressing sequelae of wound infection, gangrene, and death. Therefore, following Pasteur's announcement and during the incumbency of the Edinburgh chair (1869-77) he was largely concerned in working out the principles and details of the antiseptic methods which revolutionized surgical procedures. Pasteur's work found Lister in an advantageous position to appreciate the importance of his work as it related to wound infection. Lister's contributions were no accident but were made possible by his training in basic science, and found him with the tools in his hands to apply Pasteur's great discovery to the prevention and treatment of wound infection.

Due largely to the extraordinary work of Pasteur and Lister and augmented materially by further contributions in bacteriology, pathology, physiology, and chemistry by Koch, Virchow, Johannes Mueller, Claude Bernard and Liebig, antiseptic and then aseptic surgery became firmly established in the last half of the 19th Century. During the lifetime of most of us there has developed with startling rapidity the extension of surgery to every part of the body, bringing new problems for solution, both fundamental and technical, which has resulted in the greatest wave of specialization surgery has ever seen. In addition to the older specialties, neurosurgery, thoracic surgery, plastic surgery, vascular surgery, and reconstruction surgery have made progress that has been phenomenal. As one would expect, the most important contributions have come from men who have had the broadest training in general surgery, surgical principles and in the basic sciences. All of us have been witnesses and many of you have been participants in the advance in our knowledge of shock, hemorrhage, coagulation of the blood, maintenance of fluid balance, blood electrolytes and plasma protein, wound healing, transplantation of tissues, treatment of infections, decompression of the gastro-intestinal tract, surgical bacteriology, pathology and growth phenomena of tumors of the bone, gastro-intestinal tract, lung, and ductless glands. We have also witnessed visualization of the gastro-intestinal, biliary and urogenital tracts, blood vessels, lung and brain, but to mention some of the most important contributions.

The wide diversities of interest or specialism in surgery is but a natural outcome of its increased horizon and to maintain a proper prospective in its proceedings, the American Surgical Association has in recent years elected to its membership leaders in the various fields of special surgery. This policy should be continued for it affords this Association an opportunity to assume leadership in influencing further and proper development of specialized surgery. The danger of inbreeding specialism rears its head where specialists train specialists to the point of attrition of sound general principles. This can be avoided by insisting that specialism should be synonymous with maturity based on training in the fundamentals both scientific and technical, which so often leads to advance in knowledge.

The establishment of American Boards for certification of specialists surely had these principles in mind. In General Medicine, the requirement of broad training in general medicine before certification of specialists in cardiology, gastro-enterology, allergy, *etc*, must be preceded by certification by the Board of General Medicine. In surgery, however, the only special group required to have prior certification in general surgery are the proctologists. This does not and should not infer that the surgical specialty boards are not in complete accord as to the value of training in the basic sciences and principles of surgery. It does indicate, however, that we have gone our respective ways without having established a common denominator in requirements of basic training which is essential to all surgery. Could we not with profit to the future value of our surgical certifying boards meet together with an object of unifying our standards for surgical training and to take a firm position against the establishment of additional specialty boards until we have well integrated our present problems. As a first step in indicating our mutual belief in the value of training in the basic sciences, would it not be well to consider giving a single examination for all the surgical specialty boards covering principles of surgery as wound healing, hemorrhage, coagulation of the blood, thrombosis, anesthesia, surgical infections, fluid balance, as well as concepts of anatomy, physiology, chemistry, bacteriology, and pathology as applied to surgery in general. This examination would be but a preliminary requisite to the other examinations required and given by the several surgical specialty boards but would at once tend to unify our requirements in the fundamentals. I am sure we are all interested, first of all, in developing sound surgeons whose subsequent interest in special fields will be tempered with breadth of vision so essential to sound progress and the establishment of new frontiers. As an encouraging beginning, the American Boards of Orthopedic Surgery and General Surgery are now discussing the desirability of having a single preliminary examination in fundamentals which candidates must pass before taking the further examinations required by each of the two Boards.

As an added impetus to keeping our medical instruction as well as our specialties firmly based on the fundamental sciences I have felt for a long time that our medical curriculum should be reorganized to still further merge

the preclinical and clinical years. Theory and practice could well be closer integrated. As we now plan to give our most promising residents and associates additional training in the fundamental sciences so that they may have at their command the science methods so necessary in the study of basic aspects of disease, why should not the fundamental science departments in turn send one or more of their well trained young men into the wards of our teaching hospitals? There they would find already established for study living pathology of tumor growth, ulceration of the gastrointestinal tract, stone formation, circulatory disease, problems relating to ductless glands, anesthesia, and all varieties of infections, to mention but a few of the problems awaiting solution. The stimulating and regulating effect of the study of disease by clinician and fundamental scientists working side by side is well known to medical lore. One has but to peruse that delightfully written "Short History of Cardiology," by James B. Herrick, to appreciate the rôle that anatomy, pathology, physics and clinical bedside knowledge has played in intimate teamwork in advancing our knowledge and recognition of diseases of the heart and circulatory system. After describing the mutual stimulation afforded to Rokitsansky, the pathologist, and Skoda, the clinician, in their work, he quotes Rokitsansky's remarks on relinquishing the chair of pathology to the effect that his work in pathologic anatomy was only the foundation for scientific investigation in the sphere of medicine and a basis for a science of pathologic physiology.

The classic study of the physiologic aspects of arteriovenous aneurysm, by Sir Thomas Lewis, was carried out on patients. The outstanding physiologic contributions of Ivy, Mann and Best on the stomach, liver and blood coagulation, have enlisted the enthusiastic cooperation of the clinical departments and have pointed the way to further fact-finding studies in which scientific laboratory methods can be applied to the living patient.

It has never seemed to me entirely sound to have our science departments so often divorced from our teaching wards. In clinical teaching we have long since abandoned the dry quiz class exercises dealing with theory and more and more have introduced our students to patients in the wards in whose study and care they have taken an increasing part. In addition to the clinical investigation carried on by our own staff men in our hospitals and laboratories, would it not be helpful and stimulating to student, staff and science worker alike to have the latter also carrying on investigative work in our hospital wards in the field of his choice? As Helmholtz, the eminent physiologist and physicist said: "The purpose of science is to comprehend reality, for the investigator wishes to know what his work has done for the great problems of human life." It would be hard to deny that it would be profitable to bring the fundamental study of anatomy closer to clinical medicine. It is my impression that there are relatively few teaching hospitals where the bacteriologic study of surgical infections and so-called routine bacteriologic examinations reach a high level of exactitude. It is not possible in every clinical department to have clinicians fundamentally trained and

with sufficient free time to adequately cover the possibilities for study of disease from the anatomic, physiologic, bacteriologic, chemical and pathologic standpoints, and it seems logical to me to develop more of an overlap of interest in problems of the sick patient between clinical and science departments. I venture to suggest that this closer integration between theory and practice in medicine would be easier to attain if the heads of our science departments were doctors of medicine as well as holders of degrees in their respective science departments.

In the post-war days, when funds for graduate training will undoubtedly be less, it would also be economically sound to promote an overlap in the interests and activities of clinical and fundamental science departments which would in no way interfere with their basic functions but which would promote an even exchange of personnel who are interested in investigation. The value of such contacts to the student clerk in the ward would surely broaden his viewpoint and emphasize the importance of scientific companionship in care of the patient and study of his problems.

It is significant that other professions are experimenting with the idea of bringing their students studying theory into contact with practice. For some years the University of Cincinnati has sent their student engineers from a period of work in college out into industry for a few months and has then brought them back to the laboratory. Northwestern University has recently dedicated a large engineering school to that system of instruction. Mr. Kettering, of the General Motors research staff, speaking on that occasion, emphasized the importance of this principle due to the variations occurring in the application of theory to practice as well as to the understanding of the human elements involved. Basic advances in medicine in the past have been the result not only of creative but well trained minds. It is probably beyond human understanding to develop the former but it is possible to afford opportunities for sound training in the fundamental sciences as well as in technical fields.

It is my thesis that in the difficult post-war days, a large share of our funds and efforts should be expended in giving such opportunities to as many worthy candidates as possible, that our surgical specialties should mutually maintain a broad base in fundamental science requirements in an effort to keep their viewpoint a wide one. It is my hope that we may seriously discuss the feasibility and desirability of bringing theory and practice closer together in our medical curriculum.

The long, hard grind to obtain a sound training may discourage some but the stout heart which condones no short cuts will recognize the advantage of quality in training. The young man planning for his graduate training in surgery should be helped to realize how important it is that he should come into active participation in clinical surgery not only with a knowledge of his subject from the diagnostic and technical side but should bring as a part of his tools for work a special knowledge of one or more of the fundamental sciences of medicine which at once will give him a useful

background for the study of some basic aspect of disease. Equally applicable to prosecution of the war for the maintenance of freedom and our way of life as well as to our efforts to maintain and improve educational standards are the words from "Pilgrim's Progress"

"Some have thought there may be a passage forthwith to their father's house with no more hills and valleys to go over, but the way is the way and let this suffice"

In conclusion, I wish it were given to me to adequately express this Association's pride in and admiration for the young men and women of our country who, at home and in distant lands, are carrying on the finest traditions of service. A while back we were inclined to worry about our younger generation and their reactions to our unsettled society. Today we have occasion to bless them not only for their deeds but for the realization that our country and its institutions are safe indeed in their hands. Sharing fully in their valor and high service are our colleagues in medicine now in the armed forces. Today we especially salute our fellow members of the American Surgical Association who are giving all of their energy and talents to the problems centering around prevention of disease and the rehabilitation of our sick and wounded. They are writing another worthy chapter in the annals of this Association.

THE STUDY OF THE PREVENTION OF INFECTION IN CONTAMINATED ACCIDENTAL WOUNDS, COMPOUND FRACTURES AND BURNS*

FRANK L MELENEY, M D †

NEW YORK, N Y

TWO YEARS AGO, at a meeting of the American Surgical Association, a paper was read by title which outlined a plan for the study of war wounds. The plan called for ten units in as many different cities, each unit to be fully equipped with clinical and laboratory facilities to care for and study cases of civilian accidental wounds, compound fractures and burns which would simulate war casualties. All of the wounds were to be treated basically by as complete a surgical débridement as possible. The débrided tissue was to be sent to the laboratory for a complete analysis of the bacterial flora. A limited number of different kinds of local and general treatment, with a proper series of controls, were to be employed to appraise, if possible, the newer chemotherapeutic agents in the prophylaxis and in the treatment of wound infection. Careful observations and records were to be made of the course of wound healing and particularly of any evidence of infection. If infection developed, its nature and etiology was to be determined by further laboratory studies and the cause of the failure of the preventive measures was to be analyzed. A carefully prepared summary sheet was planned to contain all of the available data from the record of the case which might indicate what factors favor or minimize the development of infection. These data could then be transferred to punch cards for statistical analysis.

Six months later the plan was finally approved by the Committee on Medical Research of the Office of Scientific Research and Development but it was limited to eight of the original ten units. Before the personnel could be mobilized and equipment purchased, Pearl Harbor was bombed and we were at war. The question of the best way to use the new chemotherapeutic agents in war wounds still remained unanswered because it had been impossible to evaluate the drugs in England. The rapid evacuation of patients from hospital to hospital in a centrifugal manner had made it difficult to follow cases from the beginning to the end of the treatment.

On February 1, 1942, the eight units began to function. The original plan was altered to a considerable extent by the reports which came back from Pearl Harbor. Observers who saw the casualties there were profoundly impressed by the low incidence of wound infection, which they believed to be due to the copious application of sulfanilamide to the wounds.

* Read before The American Surgical Association, Cincinnati, Ohio, May 13-14, 1943.

† Representing the Subcommittee on Surgical Infections of the National Research Council, and the responsible investigators of the Contaminated Wound and Burn Project under the Committee on Medical Research of the Office of Scientific Research and Development, Doctors Guy Caldwell Warfield Fier, Charles Johnston Sumner Koch, John Lockwood, Perlin Long, Champ Lyons, Roy McClure, Alton Ochsner, Mont Reid and Frank Melenev, Chairman.

Our original plan called for observation on control cases without drugs and other controls receiving treatment with local bacteriostatic agents other than the sulfonamides. But, said the Pearl Harbor observers "You cannot withhold from these patients the benefit of the sulfonamide drugs"

Instead of twelve different categories to cover the whole field as we originally planned, we reduced the range of our investigation to one principle method of treatment, with one optional control. In so doing, it was recognized that we might have all of our eggs in one basket and find, after a period of time, that the basket would fall and the eggs be broken.

During the period of our delay, sulfadiazine had come into use. It was found to be less toxic than sulfanilamide, less nauseating than sulfapyridine, and less likely to block the kidneys than sulfathiazole. Its range of antibacterial activity was thought to be as wide as any of the other drugs and it was, therefore, decided upon as the drug of choice for systemic administration. For local application it was decided to use equal parts of sulfanilamide and sulfadiazine powder on the theory that the sulfanilamide in a concentration of 1000 mg % would be active for several days before it was absorbed. The more slowly absorbable sulfadiazine would then continue to act over a long period of time, possibly as long as ten or fourteen days.

Seven of the eight units undertook to study all three of the major categories of injuries, namely, soft-part injuries, compound fractures and burns, while the eighth concentrated on burns.

With regard to burns there were strong advocates for three different methods of treatment. These were (1) the tannic acid method, (2) the vaseline compression dressing method, and (3) the sulfadiazine in triethanolamine spray. A fourth experimental method was permitted each of the units.

No attempt was made to dictate procedures. The surgeons were directed to perform as complete a débridement of the wounds as possible, but beyond that they were given full liberty to decide other details of the treatment. In those units in which non-drug treated controls were used, every care was taken that there should be no selection of control or treated cases but that they should alternate regularly.

Great care was taken to make accurate observations and careful records so that we would know just how the cases were handled. It was decided that all those having the care of the patient should determine as a group, whether or not infection had developed and whether it was trivial or serious. The criteria of infection included not only the bacteriologic findings but the clinical evidence of inflammation, namely, redness, swelling, pain, fever, undue exudate, necrosis of tissue, or delay of wound healing. There may have been differences of opinion on individual cases but we believe that, on the whole, the personal equations have been pretty well neutralized. As the responsible investigators of the different units have gathered in Washington to talk over their experiences, it has been obvious that all of the units have had similar experiences and remarkably similar results.

The summary sheets were completed as soon as possible after the healing of the wound had taken place. Preliminary reports were sent in on all com-

pound fractures within two months and changes have been incorporated later in the record if infection or delayed bone healing supervened

As the records came in, the data were transferred to punch cards and were then analyzed according to common factors. For the most part, it was possible to divide the case into two or three groups within each category, for example, they were separated into those having maximum and those having minimum gross contamination and similarly maximum and minimum tissue damage. Those operated upon within three hours were compared with those operated upon after three hours. With regard to wound closure, three groups were compared, namely, wounds left open, wounds partially closed and wounds completely closed. And so forth with all of the factors which we thought might play a role in favoring or minimizing the incidence of infection. In each of these groups the number and percentage of trivial and serious infections have been determined. As the summary sheets steadily accumulated in the central office the number of cases in each group steadily mounted and it became necessary to apply the statistical formula which biostatisticians use to determine whether percentage differences are statistically significant or may be due merely to chance.

The records from the first 1500 cases have been summarized in the present report. These include 682 wounds of the soft parts, 471 compound fractures, and 347 burns. Each group has been dealt with separately, although they have much in common when it comes to a consideration of those factors which tend to favor or minimize the incidence of infection. These factors inherent in wounds and burns have been well known to surgeons for a long time, and they have known many ways of aiding nature to ward off infection. A study of this kind would not be warranted at this time if some new method of combatting infections had not come to light which must be thoroughly evaluated with respect to war wounds and burns.

With the advent of the newer chemotherapeutic agents, the surgeon now has the opportunity of applying to the wound surfaces or administering internally a bacteriostatic agent. However, these may not be used without some risk of toxicity to the blood forming organs, liver and kidneys. Furthermore, it is known that certain conditions may be present in wounds and burns which may inhibit the bacteriostatic action of these drugs.

The results are shown in the accompanying table.

TABLE I
INCIDENCE OF INFECTION IN 1500 CASES DIVIDED INTO THE THREE MAIN CATEGORIES
Soft-Part Wounds

	Totals	% Infected	
Totals	682		
Serious infection	38	5.6	
Trivial infection	74	10.9	16.5
<i>Compound Fractures</i>			
Totals	471		
Serious infection	55	11.7	
Trivial infection	47	10.0	21.7
<i>Burns</i>			
Totals	347		
Serious infection	66	19.0	
Trivial infection	80	23.1	42.1

SOFT-PART WOUNDS

We find an incidence of 16.5 per cent of infection in soft-part wounds as a whole with twice as many trivial as serious infections. There is no clear-cut division between these two groups, for one shades off into the other.

TABLE II
PERCENTAGE OF INFECTION IN COMPARABLE GROUPINGS IN 682 SOFT-PART WOUNDS

	Totals	% Infected	
		Serious	Trivial
Shock	166 [#]	10.8*	13.8
No shock	509 [#]	3.9 [†]	10.0
Maximum tissue damage	340 [#]	8.0*	13.2
Minimum tissue damage	341 [#]	3.2*	8.5
Maximum gross contamination	245	7.8 [†]	13.9
Minimum gross contamination	437	4.4*	9.2
Operation before three hours	413 [#]	3.4*	10.7
Operation after three hours	266 [#]	9.0*	11.3
Maximum washing	178 [#]	8.4*	18.0
Minimum washing	502 [#]	4.6*	8.4
Complete débridement	431 [#]	4.6*	9.2
Incomplete débridement	216 [#]	7.4*	14.4
Wound left open	57	1.8*	10.5
Partial closure	58	12.1*	19.0
Complete closure	567	5.3*	10.1
Partial or complete closure with tension	55 [#]	14.7*	16.4
Partial or complete closure without tension	375 [#]	5.3*	8.8
Tendon repair	114 [#]	9.6*	10.5
No tendon repair	403 [#]	2.7*	11.2

[#] Data incomplete

* Statistically significant

Serious infections are associated significantly with shock, with heavy gross contamination and with severe tissue damage. Operation after three hours, incomplete débridement and prolonged washing are associated with a high incidence of infection. The figures for prolonged washing are surprising. These results may indicate that washing of a dirty wound before débridement may disseminate the organisms throughout the wound, and irrigation all during the operation may wash organisms in from the surrounding skin and further damage tissue. Wounds which are partly closed showed a higher figure than either those left open or those completely closed. This may mean that partial closure frequently had sutures under tension or the surgeon had grave doubts that the wound should be closed. In this series the completely closed wound cases were ten times as numerous as those left open or those partially closed. Closure under tension, when that was noted, frequently seemed to play a major rôle in the occurrence of infection. Tendon repair cases show a high rate of infection and the sulfonamide drugs have not lowered this rate. By every method of grouping these cases from the point of view of chemotherapy, we can find no evidence that either sulfanilamide or equal parts of sulfanilamide and sulfadiazine locally or sulfadiazine generally with or without the local use of drugs have cut down the incidence of local infection. It is true, however, that the incidence of septicemia or of death is extremely low in this series and it may be fairly stated that the spread of infection from the local site has been minimized, for

TABLE III

INCIDENCE OF INFECTION IN DRUG TREATED CASES AND IN COMPARABLE CONTROLS IN 682 SOFT-PART WOUNDS

	Totals	% Infected	
Local Sulfanilamide and Sulfadiazine in equal parts	188		
Serious infection	8	4	3
Trivial infection	23	12	2
Local Sulfanilamide	197		
Serious infection	13	6	6
Trivial infection	31	15	7
Total local Sulfonamide	397		
Serious infection	23	5	8
Trivial infection	54	13	6
No local drug	281		
Serious infection	14	5	0
Trivial infection	20	7	1
General Sulfadiazine	452		
Serious infection	27	6	0
Trivial infection	56	12	4
No general Sulfadiazine	223		
Serious infection	10	4	9
Trivial infection	17	7	6
General Sulfadiazine without local Sulfonamide	81		
Serious infection	6	7	4
Trivial infection	4	4	9

cases which have become infected either during the administration of drug or without preliminary drug treatment have all been given systemic sulfonamide treatment, if, and when, they could tolerate it

TABLE IV
SOFT-PART WOUNDS

Total 682	Death from Infection, 2—Both Wounds Closed	
	Case I	Case II
Lesion	Avulsion of scalp	Stab wound of chest, abdomen diaphragm stomach
Operation	Debridement, closure with tension	Debridement, closure without tension
Primary drug	0	Sulfanilamide locally Sulfadiazine generally.
Secondary drug	Sulfadiazine	Sulfadiazine
Cause of death	Meningitis	Empyema
Day of death	24th +	3rd
Principle organisms	Coag -pos staph, <i>B. pyocyaneus</i>	Hemolytic strept Group F

There were only two deaths from infection, or 0.3 per cent. One developed meningitis on the 24th day after an avulsion of the scalp. No primary drugs were used. The other died on the third day following a stab wound of chest, diaphragm and stomach from a Group F hemolytic streptococcus emphyema. Primary drug was used, both locally and generally.

TABLE V

SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCI IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Hemolytic Strep	36	16	7	5	40	0	12	41	6
Gen'l sulf	29	20	7	5	40	0	11	36	4
No gen'l sulf	7	0	14	0	0	0	1	100	0
Local sulf	26	15	4	4	25	0	11	36	4
No local sulf	10	20	0	1	100	0	1	100	0

TABLE VI

SHOWING THE NUMBER OF CASES YIELDING COAGULASE POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Coag -Pos <i>Staph Aureus</i>	58	8 6	19 0	15	20 0	60 0	44	20 4	59 1
Gen l sulf	46	8 7	21 8	14	14 3	64 3	36	22 2	61 2
No gen l sulf	12	8 3	8 3	1	100 0	0	8	22 5	50 0
Local sulf	45	6 7	22 2	14	14 3	64 3	34	14 7	64 7
No local sulf	13	15 4	7 7	1	100 0	0	10	40 0	40 0

TABLE VII

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Pathogenic Gram-neg Aerobic Bacilli	162	8 6	12 3	27	33 3	37 0	19	36 8	52 6
Gen l sulf	114	9 6	14 0	21	33 3	42 9	16	31 2	56 3
No gen l sulf	48	6 3	8 3	6	33 3	16 7	3	66 7	33 3
Local sulf	93	10 7	17 2	21	33 3	42 9	14	28 6	57 1
No local sulf	69	5 8	5 8	6	33 3	16 7	5	60 0	40 0

TABLE VIII

SHOWING THE NUMBER OF CASES YIELDING *Clostridium welchii* IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft-Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
<i>Clostridium Welchii</i>	97	8 2	17 5	10	40 0	20 0	6	33 3	33 3
Gen l sulf	75	10 7	16 0	10	40 0	20 0	6	33 3	33 3
No gen l sulf	22	0	22 7	0	0	0	0	0	0
Local sulf	67	10 4	16 4	9	44 4	22 2	6	33 3	33 3
No local sulf	30	3 3	20 0	1	0	0	0	0	0

TABLE IX

SHOWING THE NUMBER OF CASES YIELDING ANAEROBIC COCCI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES WITH AND WITHOUT SULFONAMIDE TREATMENT

Soft Part Wounds—682

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Anaerobic Cocci	70	7 2	12 9	5	60 0	20 0	3	33 3	66 7
Gen l sulf	40	5 0	10 0	4	50 0	25 0	3	33 3	66 7
No gen l sulf	30	10 0	16 7	1	100 0	0	0	0	0
Local sulf	35	5 7	11 4	4	50 0	25 0	3	33 3	66 7
No local sulf	35	8 6	14 3	1	100 0	0	0	0	0

The bacteriology has been interesting and important. We must remember that these are almost always mixed cultures and bacterial synergisms and antagonisms may play an important rôle but certain organisms stand out as most important, namely the hemolytic streptococcus, the coagulase-positive staphylococci, the pathogenic gram-negative bacilli, the Welch bacillus and the anaerobic cocci. These were found in the débrided tissues in many cases but in the great majority they did not persist, being removed either by the operative procedures or by the local defenses of the body or by both. However, in many instances organisms of these same groups appeared in later cultures in cases in which they were not originally found. These may have been there originally and were not recovered, but the chances are that they often represented secondary contamination occurring during the course of treatment, particularly in open compound fractures and burns. We were anxious to find out whether the sulfonamides would eliminate the organisms found in the débrided tissue and prevent secondary contamination and infection, but such was not the case. There was no greater reduction of the original contamination nor of the secondary contamination in the drug treated cases than in the controls which received no drug.

COMPOUND FRACTURES

In discussing the results in compound fractures it should be clearly understood that we have only considered this problem from the point of view of infection. It is recognized that a compound fracture has two elements, namely, the break in the bone and the wound of the surrounding soft parts and skin. The end-result desired is a normally functioning member, with firm bony union and freely contracting muscle around the bone and freely moving joints on either end of the fractured bone. This end-result is materially altered or delayed by infection within or around the bone or by infection in the soft parts. Infection is more likely to occur and is much more serious when it develops in a compound fracture than when it develops in a soft-part wound. Bone is less resistant to infection than soft parts and it is frequently cut off from its blood supply either as a loose fragment or as the exposed end of the shaft which has been stripped of its periosteum. Infection may either develop at once, within the first few days after the injury, or start up with the first efforts to obtain full motion of the part, or lie dormant for months after the wound has apparently healed and suddenly or gradually develop after some trauma or some general lowering of resistance.

In this series the compound fractures have been grouped in many different ways according to the common factors and, while in every category there are other factors at work beside the common factor, this seems to be the only way in which the significance of these factors can be determined.

TABLE X

PERCENTAGE OF INFECTION IN COMPARABLE GROUPINGS IN 471 COMPOUND FRACTURES

	Totals	% Infected	
		Serious	Trivial
Major fracture	275	14.2	8.0
Minor fracture	196	8.2	12.7
Shock	112 [‡]	19.6*	8.0
No shock	354 [‡]	9.3*	10.7
Maximum contamination	234	16.7*	8.5
Minimum contamination	237	6.8*	11.4
Maximum tissue damage	360	13.6*	11.1
Minimum tissue damage	111	5.4*	6.3
Wound left open	91 [‡]	16.5*	11.0
Partial closure	73*	19.2*	11.0
Complete closure	304 [‡]	8.6*	9.5
Fracture plated	54 [‡]	27.8	9.3
Plaster immobilization	215 [‡]	14.0	6.5
Skeletal traction	62 [‡]	17.7	9.7

[‡] Data incomplete

* Statistically significant

We find that shock, maximum gross contamination and maximum tissue damage are associated with the most serious infections. Early operation, complete wound debridement and prolonged wound washing do not appear to play as important rôles as with soft-part wounds. The incidence of serious infections, when the wounds are closed completely, is less than when the wounds are left open or are partially closed. This has been a consistent finding throughout the study and it seems to be reasonably explained when we consider that wounds which are left open, with fractured bone exposed, are subject to secondary contamination over a fairly long period of time before the bone has had a chance to grow a protective covering of granulation tissue.

TABLE XI

INCIDENCE OF INFECTION IN DRUG-TREATED CASES AND IN COMPARABLE CONTROLS IN 471 COMPOUND FRACTURES

	Totals	% Infected	
		Serious	Trivial
Local sulfanilamide and sulfadiazine in equal parts	145		
Serious infection	18	12.4	
Trivial infection	26	17.9	30.3
Local sulfanilamide	172		
Serious infection	20	11.6	
Trivial infection	11	6.4	18.0
Total local sulfonamide	225		
Serious infection	41	12.6	
Trivial infection	37	11.4	24.0
No local sulfonamide	141		
Serious infection	14	9.9	
Trivial infection	7	5.0	14.9
Total general sulfonamide	359		
Serious infection	47	13.1	
Trivial infection	38	10.6	23.7
No general sulfonamide	112		
Serious infection	8	7.1	
Trivial infection	9	8.0	15.1
General without local sulfonamide	38		
Serious infection	6	15.8	
Trivial infection	2	5.3	21.1

The combined local and general, or the general, use of sulfonamides alone have not lowered the incidence of local infection. Although there

INFECTION IN WOUNDS AND BURNS

TABLE XII
COMPOUND FRACTURES

Total 471	Deaths from Infection 2	
	Case I	Case II
Bones	Tibia fibula hum	Femur, tibia and fibula
Operation	Partial closure without tension Plaster	Partial closure with tension Plate
Primary drug	Local sulfanilamide General sulfadiazine	Local sulfanilamide General sulfadiazine
Day of death	9th	110th
Principle organisms	Coag -pos staph green strept <i>Cl bifementans</i>	Coag -pos staph <i>E coli</i> <i>B pro-</i> <i>teus</i> , <i>B pyocyaneus</i> <i>Cl sporo-</i> <i>genes</i>
Cases requiring because of infection		
	(a) Excision of dead tissue	5
	(b) Wound to be opened for drainage	11
	(c) Incision for drainage	15
	(d) Amputation	16

are only two cases which died as a result of infection, and these yielded no positive blood cultures, a fair number of cases needed secondary surgical procedures because of wound infection—5 required excision of dead tissue, 11 had to have wounds opened up, 15 required a new incision for drainage of abscesses, and 16 needed secondary amputation. The two fatal cases both had local as well as general prophylactic sulfonamide therapy.

TABLE XIII
SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCUS IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Hemolytic Strep	34	20.6	17.6	8	37.5	25.0	17	35.3	23.5
Gen l sulf	24	29.1	20.8	7	52.9	28.6	14	28.6	21.4
No gen l sulf	10	0	10.0	1	0	0	3	66.7	33.3
Local sulf	18	22.2	27.8	4	0	50.0	13	23.1	23.1
No local sulf	16	18.8	6.2	4	75.0	0	4	75.0	25.0

TABLE XIV
SHOWING THE NUMBER OF CASES YIELDING COAGULASE-POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE, THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Coag -pos <i>Staph aureus</i>	41	12.2	19.5	12	33.3	50.0	36*	44.5	21.8
Gen l sulf	32	12.5	25.0	11	27.3	54.6	33	42.4	30.3
No gen l sulf	9	11.1	0	1	100.0	0	3	66.7	0
Local sulf	30	10.0	26.6	10	20.0	60.0	33	42.4	30.3
No local sulf	11	18.2	0	2	100.0	0	3	66.7	0

TABLE XV

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM-NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS NEW CULTURES WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Pathogenic Gram -neg									
Aerobic Bacilli	78	23 1	11 5	12	50 0	25 0	28	28 6	25 0
Gen I sulf	58	27 6	10 3	7	85 7	0	19	31 6	26 3
No gen I sulf	20	10 0	15 0	5	0	50 0	9	22 2	22 2
Local sulf	54	26 0	9 3	6	83 3	0	18	33 3	22 2
No local sulf	24	16 7	16 7	6	16 7	50 0	10	20 0	30 0

TABLE XVI

SHOWING THE NUMBER OF CASES YIELDING *Clostridium welchii* IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
<i>Clostridium Welchii</i>	90	21 1	11 1	11	45 5	0	6	33 3	16 7
Gen I sulf	68	22 1	13 2	11	45 5	0	4	25 0	25 0
No gen I sulf	22	18 2	4 3	0	0	0	2	50 0	0
Local sulf	61	19 7	13 1	9	33 3	0	3	33 3	33 3
No local sulf	29	24 1	6 9	2	100 0	0	3	33 3	0

TABLE XVII

SHOWING THE NUMBER OF CASES YIELDING ANAEROBIC COCCI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Compound Fractures—471

	Débrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Anaerobic Cocci	55	3 6	14 5	3	0	33 3	6	33 3	16 7
Gen I sulf	41	4 9	17 1	3	0	33 3	4	25 0	0
No gen I sulf	14	0	7 1	0	0	0	2	50 0	50 0
Local sulf	32	6 2	21 9	3	0	33 3	4	25 0	0
No local sulf	23	0	4 3	0	0	0	2	50 0	50 0

With regard to the bacteriology it is seen that there is a higher proportion of cases yielding hemolytic streptococci, coagulase-positive *Staphylococcus aureus* and *Cl welchii* than in the soft-part wounds and, furthermore, that they more often persisted and more often appeared as new cultures. The pathogenic gram-negative aerobes did not appear as often initially but appeared anew in a much higher percentage in compound fractures than in soft-part wounds. The sulfonamides did not particularly favor their elimination or prevent their secondary development in the wounds.

BURNS

The infection rate in burns is very disturbing, particularly in deep second and third degree cases.

INFECTION IN WOUNDS AND BURNS

TABLE XVIII

PERCENTAGE OF INFECTION IN COMPARABLE GROUPING IN 347 BURNS

	Totals	% Infected	
		Serious	Trivial
Second degree	192	10 4*	14 1*
2nd and 3rd degree	155	30 3*	34 2*
Area < ten per cent	180#	10 0*	23 2
Area > ten per cent	166#	28 9*	22 9
Shock	45#	40 0*	13 3
No shock	292#	15 8*	23 3
Maximum contamination	154	27 3*	27 3
Minimum contamination	193	12 4*	19 7
Maximum tissue damage	213#	23 0*	27 7
Minimum tissue damage	131#	12 2*	16 0
Minimum washing	156	11 5†	22 4
Maximum washing	191	25 1*	22 6

Data incomplete

* Statistically significant

As with the other groups of cases, the extent of the involved area, the depth of the injury, the intensity of gross contamination and tissue damage run parallel with the percentage of infections

TABLE XIX

PERCENTAGE OF INFECTION OCCURRING WITH VARIOUS FORMS OF TREATMENT IN 347 BURNS

	Totals	% Infected	
		Serious	Trivial
Tannic acid without sulfonamide	20#	30 0	35 0
Quebracho-tannin	11#	54 5	18 2
Tannic acid with sulfonamide	23#	21 7	26 1
Compression dressings	81#	13 6	21 0
Zinc peroxide with pressure	15#	0	20 0
Saline compresses with pressure	34#	14 7	20 6
Total sulfadiazine ointment	65#	15 4	29 3
Total sulfadiazine spray	37#	5 4	29 7
Total sulfonamide film	16#	31 3	25 0
Total sulfonamide powders	31#	45 2	3 2
Total local sulfonamides	172#	20 9	23 8
General sulfadiazine	141#	31 2	19 9
No general sulfadiazine	201#	10 4	24 9

Data incomplete

* Statistically significant

The methods of treatment have varied considerably and great latitude has been granted the different units to explore new fields of burn therapy. The compression dressing method has stood out as representing the greatest proportion of right principles and the lowest incidence of infection. The initial dressing containing a bacteriostatic agent has a slight but not clear-cut superiority over the simple nonadherent ointments.

In burns we have a tissue extensively damaged which may contain sulfonamide inhibitors. There is evidence that there may be greater or less absorption of the drugs from burned surfaces according to the vehicle in which the sulfonamide drugs are contained. The ideal vehicle has not yet been found. Many are being tried. The local drug action may be inhibited while the general effect may be obtained from local applications.

There were only two burn deaths in which infection played an important rôle and these were so extensive that they might have died without infection. Both had local and general sulfonamide treatment.

TABLE XX

BURNS

Total 317

Deaths from Infection 2

	Case I	Case II
Degree	2nd and 3rd	2nd and 3rd
Region	Face trunk, both arms and hands, right leg	Face trunk and all limbs
Per cent of body	60-70	60-70
Local R	Equal parts powder sulfanilamide and sulfadiazine	Fibrinogen thrombin sulfadiazine
General R	Sulfadiazine	Sulfadiazine
Day of death	5th	28th
Principle organisms	Coag pos staph, nonhemolytic strept, <i>B. pyocyaneus</i> <i>B. proteus</i>	Coag-pos staph hemolytic strept (Group D) <i>B. pyocyaneus</i> <i>E. coli</i>

TABLE XXI

SHOWING THE NUMBER OF CASES YIELDING HEMOLYTIC STREPTOCOCCI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Hemolytic Strep	18	25 0	22 9	12	50 0	25 0	34	47 1	47 1
Gen 1 sulf	28	32 1	21 4	6	66 7	33 3	13	76 9	23 1
No gen 1 sulf	20	15 0	25 0	6	33 3	16 7	21	28 6	61 9
Local sulf	29	31 0	20 7	5	60 0	10 0	12	33 3	66 7
No local sulf,	19	15 8	26 3	7	42 9	14 3	22	54 5	36 4

TABLE XXII

SHOWING THE NUMBER OF CASES YIELDING COAGULASE-POSITIVE *Staphylococcus aureus* IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THIS ORGANISM PERSISTED AND THE NUMBER OF CASES IN WHICH THIS ORGANISM APPEARED AS A NEW CULTURE WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Coag-pos <i>Staph. aureus</i>	51	21 6	31 4	25	32 0	44 0	52 ⁺	38 5	38 5
Gen 1 sulf	18	38 9	16 7	11	54 5	18 2	29	55 2	24 1
No gen 1 sulf	33	12 1	39 4	14	11 3	64 3	23	17 4	56 5
Local sulf	28	21 1	32 1	13	30 8	16 1	31	38 7	38 7
No local sulf	23	21 7	30 1	12	33 3	11 7	21	38 1	38 1

TABLE XXIII

SHOWING THE NUMBER OF CASES YIELDING PATHOGENIC GRAM-NEGATIVE AEROBIC BACILLI IN THE DÉBRIDED TISSUE THE NUMBER IN WHICH THESE ORGANISMS PERSISTED AND THE NUMBER OF CASES IN WHICH THESE ORGANISMS APPEARED AS A NEW CULTURE, WITH AND WITHOUT SULFONAMIDE TREATMENT

Burns—347

	Debrided Tissue			Persisting			New		
	Total	% Infected		Total	% Infected		Total	% Infected	
		Ser	Triv		Ser	Triv		Ser	Triv
Pathogenic Gram-neg Aerobic Bacilli	82	24 4	23 3	24	50 0	33 3	51	45 1	27 5
Gen 1 sulf	43	37 2	18 6	16	56 2	25 0	28	53 6	28 6
No gen 1 sulf	39	10 2	28 2	8	37 5	50 0	23	34 8	26 1
Local sulf	44	29 5	25 0	12	58 3	33 3	21	52 4	19 0
No local sulf	38	18 4	21 1	12	41 7	33 3	30	40 0	33 3

The bacteriologic studies reveal that many of the hemolytic streptococci persist in the burned area or come in as new contaminants in the face of local as well as general sulfonamide therapy. The staphylococci are the most numerous of the pathogens in the persistent and new cultures, but the gram-negative aerobic bacilli, particularly the *E. coli*, *B. pyocyaneus* and *B. proteus* groups, run the staphylococci a close race. If the problem of infection in burns is to be solved it must be concerned with all of these groups of organisms. Something must be sought for which will be effective in halting the growth of these organisms in the presence of the dead and damaged tissue of burns.

CONCLUSIONS

(1) Our studies have indicated the important factors concerned in the development of infection in accidental contaminated wounds and burns.

(2) We have found that the sulfonamides minimize the general spread of infections and cut down the incidence of septicemia and death.

(3) We have no evidence that they lessen the incidence of local infection when used as we have employed them.

(4) If we are going to lessen the incidence of local infection in war wounds and burns, some other forms of the sulfonamides or some other bacteriostatic agents must be found which will be effective against the contaminating organisms in the presence of damaged tissue.

DISCUSSION—DR EVARTS GRAHAM (St. Louis, Mo.) When the Committee on Surgery of the National Research Council was organized, in the spring of 1940, one of the questions which was put to it by the Surgeon-Generals of the Army and Navy was "What about the use of sulfonamides in battle casualties, in wounds?"

Shortly before this, the report of Jensen had come out about the beneficial effect, as he thought, on compound fractures of the use of sulfanilamide applied locally. In order to answer this very important question, and in order to remove impressions and emotions and other nonscientific factors as much as possible from the study, the subcommittee of which Dr. Frank Meloney has been chairman, was formed with the idea of making as satisfactory and as closely observant a study of the effect of sulfonamides on wounds which simulated battle casualties, as possible.

Now the result of this study, which was somewhat later in getting started than we had hoped that it would be because of various reasons, has, nevertheless, I think been brought to rather satisfactory conclusions which you have heard today. I say satisfactory, only from the standpoint of the fact that the study has been made most carefully by a considerable number of very competent observers, whose names have been mentioned to you.

It is unsatisfactory, in the sense that it was disappointing especially after the enthusiastic reports of the success of sulfonamides applied locally, particularly sulfanilamide, in the wounds at Pearl Harbor. I think almost everyone was led to believe that, after all, now we have a panacea which might even perhaps minimize the necessity of surgical asepsis. That is certainly not the case. The day of listerism is not yet gone. The sulfonamides will not replace surgical asepsis.

I feel that you who have not been closely associated with this work perhaps can hardly appreciate the enormous amount of labor which has gone into it. There is no other comparable study of the effect of sulfonamides on wounds anywhere in the world. There is nothing that begins to compare with the carefulness with which this study has been made. I feel that everyone, not only the American Surgical Association

and the Surgeon-Generals, but everyone, should be greatly indebted to this committee who have worked so hard for so long a period in arriving at these results which seem to be very dependable. Emotions and impressions have been eliminated, and only hard facts have been retained.

DR JOHN S LOCKWOOD (Philadelphia) I am sure that all of the collaborators would join with me in expressing here our great appreciation for the enormous amount of labor which Dr Meloney, in particular, has expended on this study. In his responsibility, he has not only had supervision of one of the major units in the project, but he also has carried the main burden for collecting and tabulating all of these statistics. The conclusions which he has presented here today are, I believe, joined in unanimously by the Subcommittee on Surgical Infections and by the other investigators.

It might be said that Dr Meloney has set an exceedingly high standard. From the very beginning he has expressed unwillingness to be satisfied with anything other than complete prevention of infection in traumatic wounds. I think all of us have hoped that that ideal might be closely approximated, but as time has gone on, we have become increasingly aware of the fact that no measure designed simply to deal with bacteria in wounds is likely completely to achieve this high ideal, unless, of course, an agent could be found which would destroy all of the contaminating bacteria.

In accounting for the failures of sulfonamide, several observations might be appropriate. First, as Dr Meloney pointed out, these infections were not for the most part, systemic, invasive infections. They were local, and the area involved in the infection in the majority of cases was closely delimited to the area of the wound. Furthermore, most of the infections—at least those that occurred in the project under my supervision—were delayed. They did not show up as acute fulminating infections, but appeared five, seven, or eight days after wound closure. The infections were most common in those wounds in which delayed healing might have been expected by reason of poor adjustment of physiologic factors. I am reminded of Arey's important monograph on wound healing, in which, after pointing out the three main phases of wound healing namely, the refractory stage, the destructive stage, and the reparative stage, he states that the critical stage of wound repair from the standpoint of infection is the *destructive* stage, and the infections that occurred in spite of sulfonamides were those that developed during the destructive phase. The factors which encouraged bacterial activity were retention of products of tissue injury, tension, and incomplete obliteration of dead space.

Furthermore, the very same factors which will tend to delay healing and complicate the wound repair, are also factors which tend to inhibit sulfonamide action. Perhaps we cannot find an ideal sulfonamide. If we find a drug which on the one hand, will not produce local foreign body reaction but will disappear from the wound, that particular drug will not be active after five, six, or seven days—the time at which many of these infections develop. In all probability we will not be able with sulfonamides to eliminate the infections which develop because of poor physiologic adjustments in the wound. We cannot expect any more of the sulfonamides than that they will delay bacterial growth under conditions where their action is not inhibited. Therefore, the outcome of this study certainly justifies a continuing recognition of the predominant importance of surgical management and of physiologic factors in relation to wound healing and wound infection. At the same time, it points out the fact that the problem of deaths from infection in traumatic wounds should be very significantly minimized with sulfonamides.

Nothing that has been said about the lack of effectiveness of sulfonamides under the conditions used in this clinical experiment, should contradict the wisdom of the practice of employing sulfonamides routinely in battle casualties, during the period between injury and the time the casualty reaches the hospital for definitive treatment. The problem there is different from the problem which we studied in these wound study projects, and if the multiplication of bacteria in the wound fluids can be delayed for even a few hours during the transport of the wounded subject from the field of injury to the hospital that should significantly reduce the likelihood of postoperative infection. This is entirely beside the point of whether or not sulfonamides should be used in the wound if, and when, the wound is closed.

We have plenty of evidence to support the wisdom of the directive, both in the

Army and in the Navy, against routine closure of traumatic wounds. If any of us needed to learn the wisdom of that decision, I think we have the evidence.

Finally, there remains every reason to believe that sulfonamide therapy properly used in cases with established infections will be definitely of value, and we now have in penicillin what appears to be an even more powerful weapon in dealing with staphylococci and *Clostridium welchii* infections.

DR MARTIN B. TINKER (Ithaca, N. Y.) Wound excision in contraindication to debridement in connection with the treatment of infected wounds has not been given the attention it seems to deserve today. On January 27, 1909, the Medical Society of the State of New York had a symposium on fractures, participated in by Drs. Harvey Cushing, Lewis Stimson, and Charles Scudder, in which I, as a young surgeon, at that time, presented a paper on contaminated compound fractures. At that session I proposed the excision of wounds, for removal of contaminated areas, without injuring important structures. Damaged areas were outlined by packing the wound first with gentian violet and pure carbolic acid, the wound was then excised, avoiding great vessels, nerves, and other important structures.

The case of a brakeman on the New York Central Railroad, who stepped in front of a slowly moving freight car loaded with brick to set the brakes, was reported. This man slipped, fell with his arm across the rail, and the loaded car passed over his arm, crushing the humerus and seriously contaminating the wound. He has a useful arm, and, although he has a flail joint, he is working for the Eastman Kodak Company, in Rochester, N. Y., at the present time. This man was demonstrated in Brooklyn, at the Academy of Medicine.

Another instance. A farmer was brought to me, whose patella was fractured by the kick of a horse. The knee joint was opened, and was contaminated with horse manure. The wound was disinfected and stained, and the wound excised and closed. The man recovered perfect use of his knee.

For experiments, the Department of Physiology, at Cornell University, gave me animals which they had chloroformed and sacrificed. Various wounds, which were definitely contaminated by resistant bacterial cultures. The wounds were excised after packing with staining and disinfecting gauze. Sections taken, and bacteriologic cultures, were proved free of contamination. These cases, with others, were also reported after World War I, at the meeting of the Military Surgeons at New Orleans, April 22-24, 1920.

The more thorough method of wound excision antedates débridement, as used by La Maitre, several years. No other method has excelled the results of wound excision for serious injuries.

DR J. ALBERT KEY (St. Louis, Mo.) I do not know where it is—it may be the unwieldiness of the series, or it may be in the punch-card system—but there is something wrong somewhere. I am perfectly convinced, and this is not emotion, that any report of a series of cases which concludes that the rational implantation of sulfonamides in contaminated wounds after they have been properly debrided does not lower the incidence of infection in these wounds, is wrong, provided the débridements and the after treatment are equivalent.

This is a monumental piece of work, backed by a lot of able observers, but I think that a few years from now they will be ashamed of their conclusions.

DR FRANK L. MILENEY (New York City, closing) I am glad to have Doctor Lockwood's assurance that the other members of the Committee and the other responsible investigators approve the presentation of the results and the conclusions which we have drawn. I might also say that I think we would all approve of his additional remarks.

With regard to Doctor Tinker's observations, I would say that the basic surgical procedure which we determined upon in the beginning, was that the wounds should be, as far as possible, excised, and that is the meaning of the word "débridement" as we have used it in this paper. Of course in many cases this had to be compromised, for one reason or another, to preserve important structures, such as blood vessels and nerves, or when, for one reason or another, an unsatisfactory or incomplete excision had to be resorted to.

With regard to Doctor Key, I can only say that in our group, at the beginning of the study, we had those who sincerely believed (and I might say that we all hoped), that these drugs would materially cut down the incidence of infection. There was no one in the group who was prejudiced against them. We were simply seeking to find out the facts, and we were not trying to prove anything.

I believe that our whole group has come to this consensus of opinion. We all believe that these figures do represent facts and tell the truth.

I greatly appreciate Doctor Graham's favorable comments. I would like to state that without the hearty support of his Committee on Surgery, this project would never have been initiated or carried forward. I believe that it is only fair to report at this time that we all feel that the most efficient unit in this study has been the one carried on here in Cincinnati by our good friends Mont Reid and William Altemeier.

BASIC PRINCIPLES IN THE TREATMENT OF THERMAL BURNS*

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GLOBAL MECHANIZED WARFARE on land, sea, and in the air has resulted in an unprecedented number of thermal burns, with a demand for an immediate answer to the confused and very debatable question of how best to treat them. This general disagreement in all the combatant countries regarding the best therapy, both as first aid and definitive, is the result of a number of factors:

I The failure, on the part of physicians and surgeons, to understand the underlying pathology and disturbed physiology of the burned individual, and the differences in the wound caused by a burn and soft-part wounds.

II The failure of those reporting the results of various types of local treatment to differentiate between the burns with superficial skin damage, so-called second degree burns, and burns resulting in areas with total skin destruction, or third degree burns. The second degree burn will heal with any form of local treatment provided the burned area is protected from contamination and the local application does not destroy the remaining epithelial covering. The latter, or third degree burn, will not heal without a prolonged period of granulation after separation of slough, and slow epithelial spread resulting in contracting scars—unless this period is shortened by skin grafting at the earliest favorable time. Infection, sepsis, hypoproteinemia and anemia are common to all untreated, or improperly treated, extensive third degree burns. Third degree and mixed second and third degree burns are the real therapeutic problems and are the criteria by which every therapy should be judged.

III Failure to appreciate the importance of trained and experienced groups of individuals interested in the care of burned patients. Special experience is expected of surgeons dealing with lesions of the various systems but the treatment of burns in the majority of hospitals is left to inexperienced interns or residents, or to the least experienced of the Junior Attendants. The Burn Committees in England, Canada and the United States are unanimous in emphasizing the importance of well-organized "burn teams" in the care of burn casualties, especially if many such cases are to be cared for in military or civilian hospitals. By burn team we mean a group made up of a general surgeon, interested in problems of infection and wound healing, a physician or technician, thoroughly trained in problems of fluid, protein and electrolyte imbalance, a general plastic surgeon—not an oral or faciomaxillary specialist—with experience in skin grafting large granulating areas, a group of trained nurses and orderlies, able and willing to stand the stress and strain of caring for severely burned patients.

* Read before the American Surgical Association, May 14 1943, Cincinnati, Ohio

IV The failure to appreciate the importance of "timing" in the sequence of events in the pathogenesis, symptomatology and treatment of severely burned patients Dr Fraser Gurd has so properly and repeatedly emphasized this most important factor in the study and treatment of burns V The one outstanding contribution to burn therapy in preventing and combatting shock is the accepted use of plasma instead of salt solution and whole blood This has reduced the mortality of burn casualties, but has saved many severely burned cases, with their late and difficult problems of treatment, which formerly died in the first day or two after the injury Late morbidity associated with anemia, hypoproteinemia, nitrogen loss with emaciation are some of the newer aspects of late survivals and will be discussed by Doctor Lund and Doctor Allen

VI The introduction of sulfonamide therapy in the treatment of burns has caused more confusion than benefit, because by so many it was looked upon, hopefully but unintelligently, as a panacea These drugs, given systemically, have undoubtedly controlled, if not eliminated septicemia and bacteremia in severe burns But the local use of the sulfonamides has not fulfilled the early promise, and the benefits of these amazing drugs will depend upon finding their optimum ionization and pH in proper media when used with sound surgical principles and with due consideration of the underlying pathology of the burned areas

Wounds resulting from burns differ from soft-part wounds in many respects As a rule they are more extensive, cause more damage to the important protecting tissue, the skin, expose a greater surface area to contamination But this injured surface is at first sterilized by the heat producing the burn and offers a better opportunity for protection from contamination if prompt and intelligent means are used to provide a protective covering over the burned surface in the initial treatment In the severe burns, with areas of total destruction of the skin, gangrene of tissue takes place which has to be sloughed off before repair by granulation and epithelization can occur If these areas are extensive, the patient develops infection, anemia, hypoproteinemia and nitrogen imbalance that is seen in any extensive process of repair following extensive gangrene of tissue

The edema of, and absorption from, a burned area differs from a soft-part wound or injury in a very interesting manner The studies of Drinker,^{1, 2} and his associates, and of McMaster,^{3, 4} have recently established experimental evidence of great importance both from the standpoint of pathogenesis and therapy In experimentally produced burns it has been shown that there is a very marked increase in the capillary permeability in the periphery of the burned area as well as in the rate of lymph flow away from this zone But of greater importance, Drinker has shown that there is a marked delay in the production or liberation of thromboplastic substance in the burned area as compared with that found in crushed tissue or soft-part wounds What the cause of this delay is, is only conjectural Does the heat of the burn affect the thermolabile thromboplastic substance?

Is it because the normally present preenzyme is destroyed and subsequently is brought to the area from other parts of the body?

It is only after eight to ten hours that the lymph flow from a burned area begins to slow down as a result of coagulation of the blood and lymph in the injured tissue. Were it not for this excessive flow of lymph and interstitial fluid away from the area, *i e*, fluid which has left the hyper-permeable capillaries to go into the intercellular spaces, a very much more marked edema of the burned area would take place. Drinker has demonstrated this by the immediate blocking of lymph drainage from a dog's paw, that has been placed in boiling water for two minutes, by injecting muscle extract into the burned area. The lymph recovered from a burned area has been shown to contain a strong vasoconstrictor substance. Studies by Drinker, and his associates, and by Alrich and Lehman, as yet unpublished, have demonstrated this vasoconstrictor substance in high dilutions. May this not be a definite cause of the secondary shock that appears in extensive burns within the first ten hours after receipt of the burn?

This increased lymph flow from the burned area for the first few hours after the receipt of the burn is of great significance in the delayed localization of infection which follows contamination of a burned surface and emphasizes the importance of taking every precaution against early contamination, especially by the hemolytic streptococcus and staphylococcus usually spread from the unsterile hands and unmasked noses and throats of those applying the initial protective dressings.

Drinker has also demonstrated that if an animal's paw, after such an exposure to boiling water, is immediately encased in a plaster of paris jacket, the edema does not take place and the lymph flow is markedly decreased as the result of this lack of edema. This, of course, means a great reduction in the plasma loss from capillary leakage into interstitial tissue spaces, and a corresponding lack of shock due to plasma loss. Gangrene of the tissues is far less in the plaster-encased paw than in the control with unbandaged paw. These studies explain the efficacy of firm pressure dressings that has been so ably emphasized by Allen and Koch,⁵ Silei,⁶ Owens,⁷ and others, and that, as a basic method of treatment is coming to be more generally accepted.

Considering these essential characteristics of the pathology of burns, the basic and simple principles of therapy may be summed up as follows. The most important early general complication is plasma volume loss as a result of plasma leakage into the interstitial spaces. This can be largely prevented by firm pressure bandaging and controlled by plasma transfusion. The prevention and treatment of shock in every severe burn, superficial or deep, is the first indication and should precede any definitive treatment. The most important local complication is infection. Inasmuch, as the burned surface is initially sterile, every precaution should be taken to prevent contamination. This can be accomplished for the most part, by adequate masking of nose and mouth and surgical asepsis in applying the initial dressings and by

leaving the wound undisturbed thereafter unless infection is evident. This initial dressing should be a fine-meshed gauze or tulle gras, impregnated with or covering a bland simple ointment or solution that will not damage the remaining epithelium. The subsequent dressings, provided the above precautions have been used, will depend upon the degree of skin damage. If total skin destruction has occurred, dressings to favor the removal of the slough as soon as possible, with skin grafting of the entire denuded granulating area at the earliest favorable time, are the essential considerations. Any form of treatment in these total skin burns which tends to seal in infection and causes a delay in skin grafting is to be wholly condemned. Here, more than in any other type of burn proper timing is the secret of success.

In estimating the relative efficacy of any new or old treatment for burns it is not the results in superficial burns but in total skin burns that should be the criterion. To date, some eighty methods of burn therapy have been published. Very few of the authors reporting their results have been intelligent or careful enough to classify their cases accurately. The studies now going on in the several Burn Projects under the National Research Council will, when assembled and analyzed, give invaluable pathologic, bacteriologic and therapeutic data on this very important but controversial subject.

There are a number of new and old methods of local treatment that are being carefully studied in the clinics where these Burn Projects are functioning. These include the sulfonamide creams and ointments, films of several kinds with and without sulfonamides, the use of the paraffin spray, and ultracentrifuged, finely divided particles of clay, known as bentonite made into water-soluble colloidal gels. Some of these preparations, when used with an understanding and appreciation of the basic principles of burn therapy, will undoubtedly prove valuable.

Of the dozens of proprietary preparations, especially those with exaggerated and fantastic therapeutic claims, the less said the better. The free advertising that some of these have been given in popular magazines is inexcusable and unfortunate, for, as always, they misinform the ignorant but innocent public.

There are a number of new and fundamentally important problems that, with further study, will undoubtedly modify and improve the treatment of the burned patient. One of these is the problem of nitrogen imbalance that is being discussed by Doctor Lund. Another is the discovery of a fluid containing protein and electrolyte, of proper molecular make-up that can be used as a substitute for plasma, with all its advantages. Recent experimental work in oral sodium therapy by Rosenthal⁸ promises interesting results in clinical cases, but there are many phases of this subject, such as the relation of serum protein loss to sodium loss and intake that need much more study before the experimental results in animals can be correlated with clinical results.

Certainly, the therapy of burns is only beginning to be understood, and

because of the great and urgent interest in the subject, much progress will be made before the war is over

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DISCUSSION—DR SUMNER L KOCH (Chicago, Ill) Some years ago Evarts Graham wrote an admirable paper entitled "Principles *versus* Details in the Treatment of Empyema" One could well apply his identical words to this discussion of burns, for in no field of surgery is the emphasis on principles rather than details more important The persistent search for some magic substance to apply to the burned area has served chiefly to befog our outlook in the problem of burn treatment and to divert our attention from the principles that Dr Whipple has stressed so clearly and emphatically I can only attempt to second his emphasis and repeat, in a little different way, what he has expressed so well

Three simple principles cannot be overemphasized, they are concerned particularly with *prevention* of complications The first principle—prevent infection, the most important *local* complication of a burn, the second, prevent loss of plasma, the most important *general* complication, the third, prevent contractures and long delay in healing—the important complications in deep burns, by replacing areas of whole-thickness loss as early as possible with skin grafts

In spite of an increasing awareness of the importance of preventing infection of the large open wound, there is not yet widespread and general recognition of the fact that the important source of infection is the uncovered mouth and nose of first aid workers, nurses and surgeons who are caring for the patient We have long been guilty of gross inconsistency in not giving the patient with an extensive open wound the protection that is deemed essential for the patient with a small wound cared for in the operating room

How *can* we prevent infection? By covering the burned area immediately with clean towels and not exposing it even momentarily until personnel with masked faces and cleansed hands are ready to carry on The practicability and helpful results of such protection were demonstrated by Churchill, and his associates at the Massachusetts General Hospital after the Cocoanut Grove fire Burned surfaces were covered with sterile towels in the emergency room, and kept covered until the patients could be cared for by masked, gowned and gloved personnel

Aldrich's studies Cruikshank's, and the observations of many other workers, show that infection of the burned surface takes place during the early period of treatment It can be prevented in the majority of cases by recognition of the important potential

sources of infection, and by protecting the open wound from them. It may well prove that the addition of sulfathiazole in an oily base, as recommended by Dragstedt, and his associates, and by Gurd, and his coworkers, at the Montreal General Hospital, or of sulfanilamide, as recommended by Evans, can be of real value in preventing development of infection, but elimination of potential sources of infection is imperative.

How can we prevent fluid loss? By providing an absorbent compression dressing over the cleansed burn surface at the earliest possible moment. Such a dressing as Siler, Reid, and their associates, and, more recently, Neal Owens and Gurd, have demonstrated so effectively, checks the oozing from the burned surface and checks and limits the fluid loss into the subcutaneous tissues. Its value is nowhere more quickly recognized than in burns of the face and extremities, where the swelling and edema that develop so rapidly under a loosely applied or a coagulant dressing can be almost completely prevented by the application of a voluminous gauze dressing compressed with the aid of an inexpensive resilient material like mechanics waste and with an elastic bandage.

If fluid must be replaced, there is no argument as to the need and value of plasma, but here, just as with infection, there can be no question as to the value of the ounce of prevention as compared with the cost, the difficulty, and the time lost in providing the pound of cure.

Concerning the third principle—early replacement of areas of whole-thickness loss—one can only repeat that no chemicals, no ointments, and no witchcraft, that have yet been devised, can produce a covering of epithelium when the whole-thickness has been destroyed. Such a raw surface, as Blair, Brown and Byars, Padgett, McClure, and practically every surgeon who has faced the problem of caring for serious burns, have repeatedly emphasized, can be covered only by the slow growth of epithelium from the periphery or by transplantation of skin. The earlier such transplantation can be successfully accomplished the sooner will the patient be well and the less will be the scar tissue contracture that invariably results from long delay in healing.

In these three simple principles—prevention of infection, prevention of fluid loss, and prevention of long delay in healing by early grafting—"hang all the law and all the prophets." If we can state them so clearly that the surgical profession will recognize their force and be guided by them, we can well leave the less important details of treatment to the imagination and initiative of the individual surgeon.

DR ALLEN O WHIPPLE (New York City, closing) I should like to refer to one problem which has been touched upon, but just to show that there is a great deal of work being done on it. That is the problem of handling the third-degree areas after slough has been removed. There is a good deal of interesting work being done at the present time with enzymes that will hasten the removal of slough. Some of it appears to be promising.

Another factor which undoubtedly will facilitate the early grafting of these granulating surfaces is the proper concentration of sodium sulfadiazine, which in the ultramicroscopic form—that is, the centrifuged form—provides a film. I have seen some cases recently, in the Harlem Hospital, where the granulating surface has been frosted with this sulfadiazine, and grafts put on that area adhere very firmly and take amazingly well.

These cases are of particular interest to me because the grafts take apparently more easily, and the donor areas treated in the same way are available in an astonishingly short time for further skin grafts. I never have seen that done before, but I saw some areas where skin grafts had been removed ten days previously, that is epithelium from those same areas were removed to provide further grafts. This is a method which, in some of the very extensive burns, is a terrible problem, because you can not get large Paget grafts from these patients, and you have to use small areas of skin. It is just an example of how these patients which survive now, and which always died previously, are providing problems that we never had before.

GELATIN AS A PLASMA SUBSTITUTE WITH PARTICULAR REFERENCE TO EXPERIMENTAL HEMORRHAGE AND BURN SHOCK[†]

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RESTORATION AND MAINTENANCE of circulating plasma volume are generally recognized as basic essentials in the prevention and treatment of shock. The successful use of crystallized human albumin indicates that the colloid osmotic pressure of plasma protein maintaining fluid distribution and plasma volume is a major physiologic factor in plasma and whole blood therapy.

In view of the difficulties of obtaining and preserving sufficient quantities of human plasma, it is natural to hope that the supply of plasma can be supplemented by a substitute which will be stable, innocuous, therapeutically effective, readily available, and reproducible with respect to its physiochemical properties. Many macromolecular colloids such as gum acacia, hemoglobin, bovine albumin, pectin, and a number of special gelatin preparations, including isinglass, have been, and are being, investigated. Hogan¹ reported, in 1915, that gelatin-saline infusions administered to patients in shock would restore falling blood pressure. Wolfson and Teller² found gelatin effective in experimental hemorrhage in the rabbit. Bayliss,³ in 1917, and Rous and Wilson,⁴ in 1918, strongly advocated the use of gum acacia, in preference to gelatin, in treatment of hemorrhage and shock. Although gum acacia has been used extensively, more recent study of its toxicity, especially with reference to its antigenicity, and its tendency to produce liver dysfunction and hypoproteinemia^{5, 6, 7} has placed it in disfavor, except in emergency conditions when no other substitute is available.

Renewed interest in the possibilities of gelatin as a blood substitute is evidenced by a number of recent investigations (Taylor and Waters,⁸ Waters,⁹ Gordon, Hoge and Lawson,¹⁰ Ivy, Greengard, Stein, Grodins and Dutton,¹¹ Little and Wells,¹² Ely and Angulo,¹³ and Grodins¹⁴

The aim of our study has been to determine (1) The response of the

[†] The Charles B. Knox Gelatin Co. and Kind and Knox Gelatine Co., Johnstown, N. Y., and Camden, N. J., supplied the material, through the courtesy of Dr. D. Tourelotte, and provided the University of Pennsylvania with a grant to defray a part of the cost of this study.

These studies were initiated by Drs. Norman E. Freeman and A. E. Schecter, who were forced to discontinue the work because of entering military service.

Preliminary reports of this work were presented at two conferences on gelatin, which were convened by the Subcommittee on Blood Substitutes of the National Research Council, in Washington, D. C., November 10, 1942, and February 23, 1943, and at the meeting of the Physiological Society of Philadelphia, April 20, 1943.

Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

normal dog to moderate and massive single and repeated infusions of bone collagen gelatin, with particular reference to general and specific toxic effects, many of which have been reported for other colloidal substances tested and used as blood substitutes, (2) the disappearance from the blood and excretion of gelatin, and (3) the efficacy of gelatin as compared with saline and plasma in the replacement of colloid osmotic pressure and plasma volume of dogs subjected to standardized conditions of hemorrhage or burn of a degree which is fatal to the untreated animal

MATERIAL AND METHODS

The gelatin used in these studies was supplied as calcium gelatinate (Lot No B78-1) produced by hydrolysis of alkali-treated bovine long-bone collagen, under controlled and standardized conditions. Our laboratory preparation was a six per cent solution in 0.85 per cent saline, sterilized by autoclave at 15 pounds pressure for 20 minutes. Aerobic and anaerobic sterility tests were uniformly negative. Although freshly prepared solutions were used routinely in these experiments, the preparation is stable for months when stored at 4°C. The solution after autoclaving has a pH of 6, a specific viscosity of 1.6 at 37°C, specific gravity of 1.024, and an osmotic pressure of 46 to 48 mm Hg.

An 0.85 per cent saline solution was made from Sharp and Dohme sodium chloride tablets especially prepared for infusion purposes. The water was single-distilled and was neither tested nor treated for pyrogenicity. Fresh solutions were filtered and autoclaved at 15 pounds pressure for 20 minutes. Heparinized or citrated, pooled dog plasma was prepared from blood drawn under aseptic conditions from healthy animals.

All dogs used in these studies were carefully selected with regard to uniformity of nutritional state, age, size and general physical condition. They were acclimated to the laboratory and maintained under observation in individual cages for a period of at least one week prior to their use, and were fed a standard diet of Purina Checkers, with an occasional supplement of table or meat scraps.

Infusions were made by needle puncture through the jugular vein, and the apparatus was chemically clean and sterile. The solutions were kept at 32° to 37°C, and were administered at a rate of 0.5 to 1.0 cc per kilogram per minute.

Blood pressure was determined in the femoral artery, by needle puncture, and mercury manometer and blood samples were withdrawn through the same needle.

Hematocrit determinations were made on heparinized blood in Wintrobe tubes, centrifuged at 2500 R P M for 30 minutes. Plasma specific gravity determinations were made by the falling-drop method of Barbour and Hamilton¹⁵. Bromsulphalein retention was determined by the method of Rosenthal and White,¹⁶ as modified by Helm and Machella.¹⁷ Prothrombin time was measured by the procedure of Quick.¹⁸ When plasma was analyzed

for plasma proteins and gelatin protein concentration, the differential precipitation of gelatin from plasma proteins was carried out with a modification of the method described by Waters¹⁶. The urine gelatin concentrations were determined by use of both tungstic and tannic acid preparation, and all nitrogen analyses were made with the aid of semimicro Kjeldahl apparatus.

EXPERIMENTAL STUDIES

I—INTRAVENOUS GELATIN IN NORMAL DOGS

1 *General Reactions*—Following infusion of 30 and 60 cc per kilogram of body weight (representing a 60 to 120 per cent increase in plasma colloid), all animals showed marked hemodilution, and with the larger doses, at least a temporary increase in blood pressure. The pulse and respiratory rates were increased for several hours after infusion. Nausea and emesis frequently occurred within two to three hours, and defecation occasionally followed within the same interval. Similar reactions often followed infusion of comparable volumes of saline or plasma. The animals usually appeared somewhat depressed and inactive for from three to six hours after the infusion of gelatin. By the following morning they were eager for food. Animals which received repeated infusions of gelatin, during a prolonged period, gained weight and remained in excellent general physical condition.

2 *Toxicity Studies*—(a) *Observations on Pyrogenicity*—In 20 experiments upon ten normal dogs the temperatures were recorded at intervals of 15 minutes, 1, 2, 3, 4, 5, 6, and 24 hours after infusion of 30 cc of gelatin per kilogram. At 15 minutes after infusion, the temperature was normal or somewhat below, with a slight increase by the second hour, reaching a peak between two and four hours, showing an average increase of 0.7°C at three hours. The range was from no change to a maximum of 1.1°C with a return to normal by the sixth hour. In four cases there was a slight temporary decrease in temperature. In four dogs infused with 10 cc of gelatin per kilogram, no temperature rise was noted.

In four normal dogs subjected to massive hemorrhage (about 50 per cent of blood volume) followed by immediate infusion with an equal amount of gelatin, the temperature of one rose 1.0°C in three hours, while that of two dogs dropped 1.1°C , and that of the fourth remained unchanged. Five dogs, bled in the same way (by needle puncture without anesthesia), and infused with sterile isotonic saline solution, showed a drop of 0.3°C in one case, no change in two, and rise of 0.9°C in the remaining two.

In view of the fact that the temperature changes with saline were similar to those with gelatin, when comparable volumes were administered, and considering the absence of temperature rises in the dogs receiving 10 cc of gelatin per kilogram, it appears doubtful that the gelatin *per se* is pyrogenic in the dog. Pyrogen tests in rabbits are in progress.

(b) *Observations on Antigemicity*—Purified gelatin is generally considered to be nonantigenic^{10, 8, 9, 10}. Sixteen normal dogs and five subjected to hemorrhage, were repeatedly infused with gelatin in amounts of 10 and

30 to 60 cc per kilogram at intervals of days, weeks and months, without showing any evidence of anaphylaxis or sensitization as judged by blood pressure, respiration and other general reactions. Urticarial skin reactions commonly observed in dogs infused with dog plasma have in no instance been noted following infusion of gelatin. Animals have not yet been tested specifically for sensitization to other bovine protein.

(c) *Hematologic Observations* Clotting Time, Pseudo-agglutination and Sedimentation Rate—The clotting time of blood from dogs at various intervals after gelatin infusion (30 cc per kilogram) was moderately increased. The average increase within 15 minutes was 16 per cent, and after three hours 30 per cent, with a return to normal within 24 hours. In two dogs subjected to triple hemorrhage and gelatin replacement, when a total of 90 cc per kilogram was infused, the clotting time was about twice normal, and a return to normal occurred within 48 to 72 hours. Changes of the same order would be expected following infusion of similar volumes of citrated or heparinized plasma.

Pseudo-agglutination of erythrocytes has been reported to follow infusions of gelatin as well as other colloidal solutions used as blood substitutes^{20, 11, 14, 10}. A pronounced increase in sedimentation rate after gelatin infusion was obvious to all who worked with the blood samples. Pseudo-agglutination and often massive clumping of erythrocytes were also apparent in the hematocrit blood samples, or when gelatin was mixed with red cells *in vitro*. However, the clumps which formed on standing were readily broken up with agitation.

Sedimentation rate determinations in gelatin-infused dogs, corrected for hematocrit changes, showed in most cases a two- to four-fold increase, with a return to normal as the gelatin disappeared from the blood stream. The increase in sedimentation rate was associated with, and apparently largely due to, the pseudo-agglutination of erythrocytes which occurred *in vivo* as well as *in vitro*. Direct observations and photomicrographs of this phenomenon *in vivo* were made by Dr. R. G. Abell, of the Department of Anatomy, using the ear-window technic in the normal unanesthetized rabbit. While the pseudo-agglutination of the red cells was present it did not appear to retard the circulation through the capillaries of the ear of normal rabbits infused with 15 cc of gelatin per kilogram. The influence of this effect of gelatin, an effect which follows the administration of certain other colloids, upon the oxygenation of the blood and the peripheral circulation of animals in shock is deserving of further study, using special gelatin preparations.

(d) *Liver and Kidney Function*—Observations on bromsulphalein retention, glucose tolerance, and prothrombin time, were undertaken as tests of liver function. Urea clearance was used as an index of kidney function.

Determinations were made before, and at intervals after, repeated weekly infusions of gelatin in 14 dogs. Three hours after each infusion of gelatin (30 cc per kilogram) a marked retention of bromsulphalein was observed, which had diminished at 24 hours, and was essentially normal at 48 hours.

GELATIN AS A PLASMA SUBSTITUTE

As illustrated in Figure 1, the degree of retention became increased, and the return to normal was increasingly delayed with each additional weekly infusion. The two dogs which showed the highest retention of bromsulphalein were selected for the illustration.

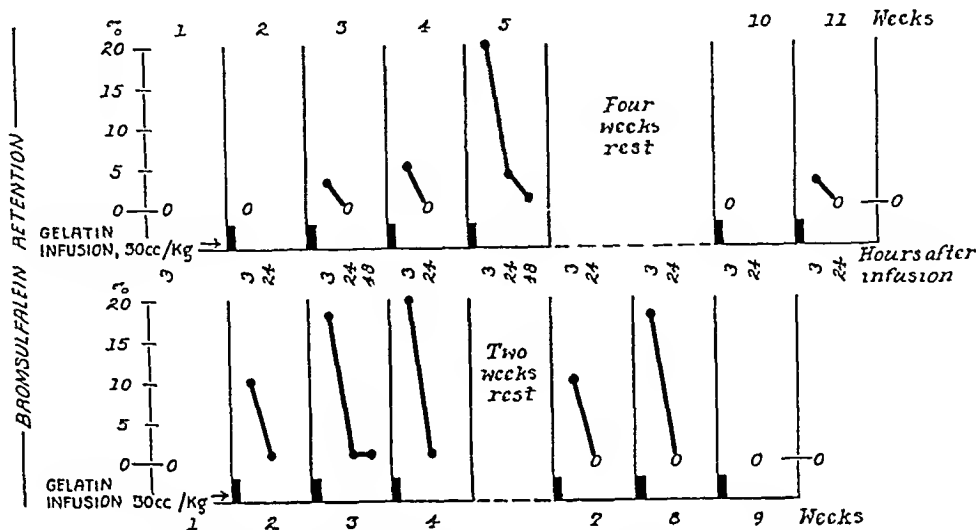


FIG 1 —Bromsulphalein retention after weekly infusions of gelatin

In animals in which the weekly infusions were suspended for a period of four or more weeks the retention of bromsulphalein after a subsequent infusion of gelatin was similar both in degree and duration to that following the first infusion of the series. However, the cumulative increase of bromsulphalein retention was present upon infusion following a rest of three weeks or less. It did not develop in dogs receiving weekly infusions of 10 cc per kilogram.

Bromsulphalein retention was also determined after infusion of 30 cc per kilogram of pooled heparinized dog plasma. Three of five dogs showed a bromsulphalein retention of as much as 16 per cent at three hours after a single plasma infusion.

The results of determinations of glucose tolerance after gelatin were variable, but no definitely abnormal curves were obtained.

The prothrombin time studies revealed normal values throughout except in one dog, which exhibited a prolonged time on two occasions as shown in Table I.

TABLE I
PROTHROMBIN TIME IN SECONDS
(Normal—under 21 seconds)

Weeks	208	243	273	296	300	
	9	17	13	9	13	Before first infusion -
2	17			17	13	Between
3	14		13	14	14	3 and 4
4	(58)		12	11	11	hours
5		14				after
6	17	13		14		weekly infusions
7	(25)	14		16		of
8		15		16		gelatin
9					14	3% of body weight
10					16	
11		16				

The explanation of the bromsulphalein retention which follows massive gelatin and plasma infusions in normal unanesthetized dogs is not clear. In view of the transient nature of the retention after gelatin and plasma, it seems permissible to conclude that the liver dysfunction suggested by retention of bromsulphalein is probably not specific to gelatin itself and presents no serious obstacle to further clinical investigation of gelatin as a plasma substitute. It should be recognized that with an infusion of 30 cc of gelatin per kilogram, the animal's plasma colloid would rise to about 160 per cent of normal unless temporary storage of gelatin or plasma protein occurred. It is during the period when a new colloid equilibrium is being reached that pseudo-agglutination of erythrocytes and retention of bromsulphalein are found. The repeated administration of smaller quantities of gelatin did not lead to cumulative retention of the dye.

(c) *Histologic Observations*—With the collaboration of Dr. H. L. Ratcliffe of the Department of Pathology, there is in progress a thorough study of tissues from normal dogs and dogs subjected to hemorrhage, and from animals which succumbed to burn shock or were sacrificed at various intervals after infusions of gelatin, saline or plasma. A detailed report will be made upon completion of the observations. For the present it can be stated that no evidence of chronic liver damage with storage of gelatin in the liver or other organs has been noted in normal dogs following single and repeated massive doses of gelatin. Tissue changes in liver, kidneys, and adrenals were only slightly more marked with gelatin than with plasma, and were definitely reversible.

II—DISAPPEARANCE FROM BLOOD, AND EXCRETION OF GELATIN

In a review of the literature on blood substitutes by Amberson,¹⁰ it is concluded from publications on the use of gelatin preparations available 20 to 30 years ago that gelatin is relatively valueless because of the rapidity with which it leaves the blood stream. Waters⁹ found calf skin gelatin to remain in the blood of infused animals much longer than does isinglass. Little and Wells¹² have recently shown that bone gelatin escapes through injured capillaries of the intestine more slowly than do the plasma proteins.

The basis of our interest in the rate of disappearance and the excretion of bone gelatin infused in normal dogs and in replacement of blood removed by a rapid massive hemorrhage was (1) To correlate blood concentrations with other studies of efficacy and reactions to gelatin, (2) to determine whether the plasma proteins depleted by hemorrhage would be replaced in gelatin-infused animals at a rate sufficient to maintain total protein concentration, colloid osmotic pressure, plasma volume and blood pressure as the gelatin concentration decreased in the blood, and (3) to correlate the disappearance of gelatin from the blood with gelatin excretion, and with plasma protein concentrations, in the attempt to obtain information relative to the fate of gelatin and the question of its utilization as available protein.

Results—Experiments on five normal dogs infused with 30 cc of gelatin

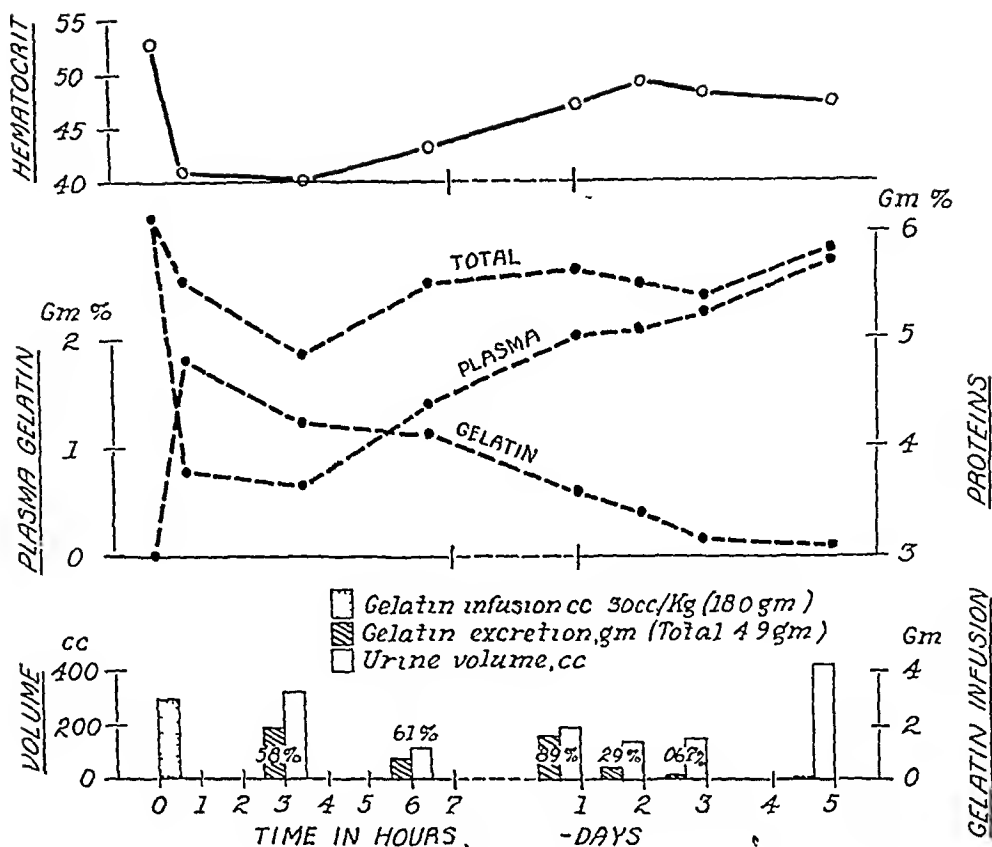


FIG 2—Gelatin disappearance from blood and gelatin excretion in normal dog

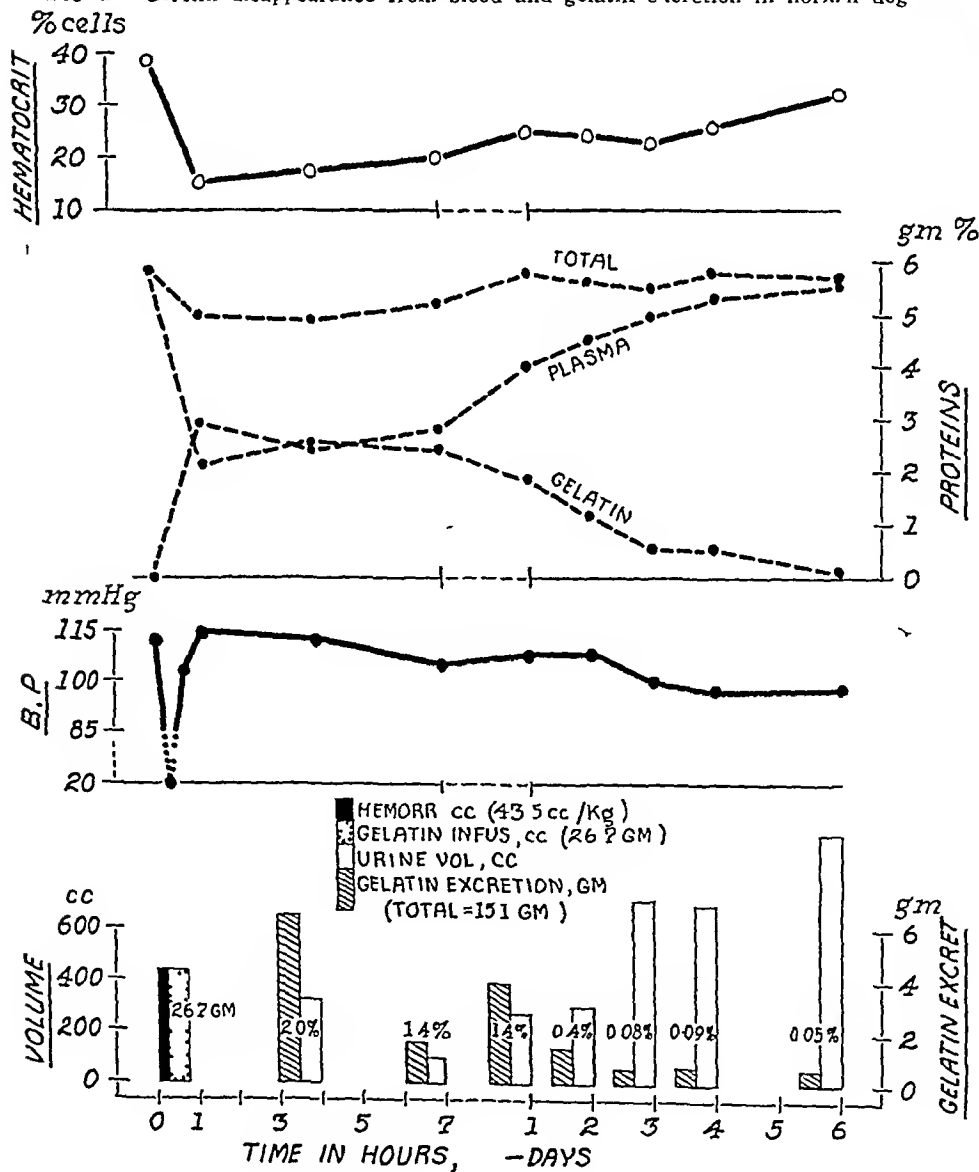


FIG 3—Gelatin disappearance from blood and gelatin excretion Single massive hemorrhage

per kilogram and on five unanesthetized dogs subjected to massive hemorrhage and infusion with a volume of gelatin equivalent to the volume of blood removed, are illustrated by representative data in Figures 2 and 3. It will be observed that a diuresis and relatively rapid excretion of gelatin occurred which decreased at six hours following infusion. Hemodilution and increased plasma volume, as indicated by hematocrit and plasma protein concentration, were well maintained in both the normal and the bled dogs, as was also the blood pressure following massive hemorrhage.

The plasma proteins were apparently replaced at about the same rate as that at which the gelatin disappeared from the blood stream. Following a brief period of osmotic adjustment to the high osmotic pressure of the infused gelatin, the total protein levels were well maintained in the experiments involving hemorrhage.

The decrease in total plasma protein concentration (including gelatin), which occurred soon after gelatin infusion, may be explained by increase in plasma colloid osmotic pressure and compensatory hemodilution, since the six per cent gelatin used has a colloid osmotic pressure about twice that of plasma. Determinations of plasma colloid osmotic pressure of blood drawn 15 minutes after gelatin replacement following hemorrhage, showed an increase of approximately 20 per cent*. Calculations indicate that the plasma volume is increased to an extent greater than the volume of fluid infused, which is in keeping with the increased osmotic pressure and consequent hemodilution from interstitial fluid.

Approximately one-half, or less, of the gelatin which leaves the blood stream is accounted for by the kidney excretion figures. The normal dog, in Figure 2, excreted 27 per cent of the gelatin infused, the dog subjected to hemorrhage (Figure 3), receiving a large amount, excreted 56 per cent. One other normal dog excreted 59 per cent.

DISCUSSION—The fate of gelatin which is not excreted remains obscure. Normal animals which received repeated weekly infusions of 30 cc of gelatin solution per kilogram showed no indication of a deposition. Parenterally administered gelatin may be partially utilized in metabolism of the body tissues, or it may enter into maintenance or replacement of plasma proteins. That parenteral gelatin is metabolized to maintain nitrogen balance or equilibrium is indicated by the work of Biunschwig, Scott, Corbin and Moe²¹. Experiments now in progress will yield additional data relative to the question of the utilization of intravenously administered gelatin.

III—STUDIES ON HEMORRHAGE

COMPARISON OF GELATIN WITH SALINE AND PLASMA

Hemorrhage, by widely different procedures and under various conditions, is commonly employed as a method by which the efficacy of potential blood substitutes may be evaluated. Unfortunately, there is no standard

* We wish to thank Doctors Tourtellotte and Williams, of the Kind-Knox Research Laboratories, for the colloid osmotic pressure determinations.

generally accepted procedure for this purpose. This fact makes difficult the comparison of results from different laboratories where various substitutes are under study.

Three bleeding procedures similar to those used experimentally by others, each of which is frequently paralleled in military or civilian injuries were employed in the following experiments. The efficacy of gelatin was compared under uniform conditions with saline or with saline and plasma. Conditions were such that few, if any, of the animals so treated would have survived without administration of one of the three infusion fluids.

I—SINGLE MASSIVE HEMORRHAGE AND IMMEDIATE INFUSION

Ten dogs were bled by arterial needle puncture, over a 10- to 15-minute interval to the point of an hunger or respiratory failure, with the blood pressure falling to 15 to 20 mm of Hg. Infusion was begun within two minutes. The volume infused was, in each case, equal to the volume of blood withdrawn. Four dogs, two in each infusion group, were given artificial respiration until the beginning of the infusion. Five animals were infused with gelatin; five were infused with saline.

Results—The data are shown as average values in Table II. All these unanesthetized dogs survived the removal and replacement of approximately one-half of their total calculated blood volume. Obviously, survival as a

TABLE II
SUMMARY OF AVERAGE VALUES—SINGLE RAPID MASSIVE HEMORRHAGE
Immediate Infusion—Saline and Gelatin

Determination	Initial	Infusion	After Infusion					
			15 minutes		3 hours		24 hours	
				% Initial		% Initial		% Initial
Blood Pressure	135	Gelatin	125	92.5	101	74.8	113	83.6
mm Hg	134	Saline	90	67.0	105	78.4	118	88.0
Hematocrit	46	Gelatin	15	32.6	16	34.8	23	50.0
% cells	44	Saline	27	61.4	27	61.4	25	56.0
Total Protein	5.83	Gelatin	5.10	87.5	4.62	79.3	5.07	87.0
gm %	5.22	Saline	3.21	61.5	3.74	71.5	4.28	82.0

criterion is of little value in determining the relative merits of infusion fluids under the seemingly severe conditions of hemorrhage in these experiments. A higher total protein concentration, a considerably greater decrease in hematocrit, and the return of blood pressure to normal within 15 minutes after gelatin infusion indicated a definite superiority of gelatin over saline in experimental hemorrhage of this type. Results from one such experiment in which gelatin disappearance and excretion were studied are illustrated by Figure 3.

Discussion—There is no general agreement in the literature regarding the efficacy of saline infusions in experimental hemorrhage^{22, 23, 24, 25, 26, 10, 11}. It should be pointed out that animals show a remarkable spontaneous physio-

logic compensation to a massive rapid hemorrhage, if the brief critical period after hemorrhage is overcome by administration of any isotonic fluid. Even though the concentrations of plasma protein may be reduced, and the effect of saline in restoration of blood volume and pressure in some conditions may be transient, the administration of saline as a temporary expedient should not be ignored.

Conclusions as to therapeutic efficacy of a number of proposed blood substitutes have been based upon survival alone, or upon blood pressure elevation following infusion of a blood substitute in animals subjected to single rapid hemorrhage^{11, 9, 27}. In those instances where the effect of saline alone was not determined under conditions of severe and otherwise fatal hemorrhage, the question may be seriously raised as to how much of the apparent influence of the blood substitute was a result of the fluid in which it was dissolved.

Under the conditions of single massive rapid hemorrhage and immediate infusion used in experiments illustrated in Table I, all of the dogs showed a definite hemodilution, increased blood pressure, and survived when saline or gelatin was infused. The early response to gelatin suggested its superiority over saline alone. However, the physiologic mechanisms of compensation were sufficient to make both groups more nearly comparable at three and 24 hours.

2—TRIPLE HEMORRHAGE AND INFUSION

A controlled triple hemorrhage procedure provided a more critical method of evaluating gelatin.

Dogs under nembutal anesthesia (25 mg per Kg, intravenously) were bled 30 cc per kilogram (approximately one-third their blood volume), and infused with an equal volume of gelatin, or saline. One hour after the first hemorrhage the animals were bled another 30 cc per kilogram, or until the blood pressure dropped to 30 mm of Hg. They were then infused. One hour later they were similarly bled and infused for the third time.

Results—When saline was infused (Figure 4) the blood pressure returned to nearly normal levels after the first infusion but was not well maintained and usually dropped to 30 mm Hg upon completion of the second hemorrhage. After the second infusion the blood pressure rarely returned to normal, and rapidly dropped to about 30 mm of Hg during the third hemorrhage. Only eight to 21 cc per kilogram, with an average of 15 cc per kilogram, could be withdrawn safely at the third bleeding, since a blood pressure below 30 mm Hg may be rapidly fatal. During the third infusion, the blood pressure rose to about 80 mm of Hg but was not sustained, even though additional saline may have been infused. However, two of the five dogs infused with saline recovered, even though the blood pressure remained at about 60 mm Hg for many hours. The plasma protein concentration was reduced to three to four Gm per cent. The hemodilution

and increased plasma volume, as indicated by hematocrit and hemoglobin were well maintained

The gelatin-infused dogs (Figure 5) were decidedly more resistant to this repeated bleeding. The blood pressure dropped but little more during the second hemorrhage than during the first, and in every case, the full

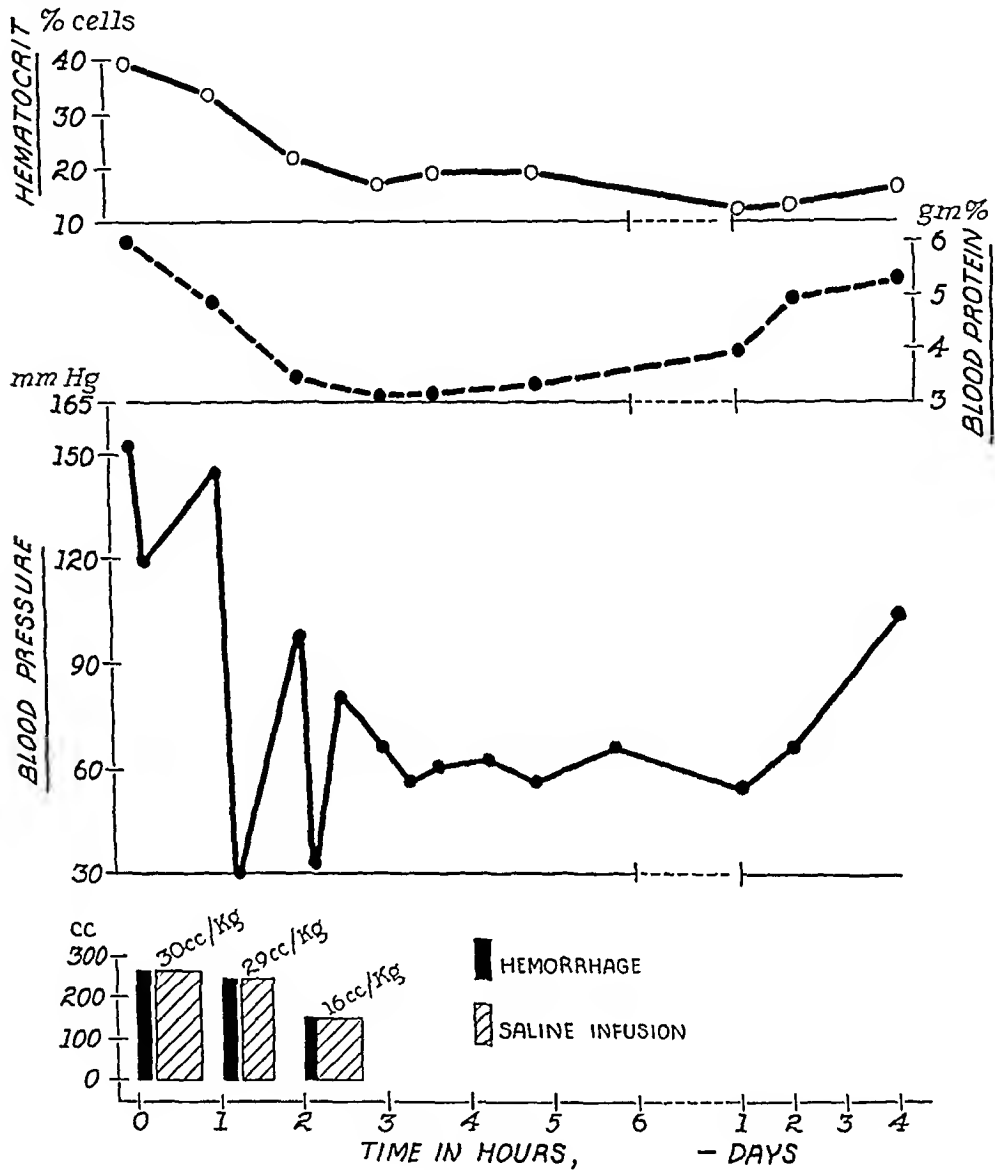


FIG 4—Saline in triple hemorrhage

30 cc per kilogram could be removed during the third hemorrhage without a decrease in blood pressure to critical levels. Three such dogs maintained a nearly normal blood pressure after the third infusion of gelatin, and recovered. With gelatin infusion the total protein levels were well maintained, and hemodilution was marked.

Two additional dogs were bled to a total of 100 cc per kilogram, in three hemorrhages, followed by immediate infusions with gelatin. These two animals succumbed within 16 hours, even though the blood pressure fell to only 46 and 68 mm of Hg, respectively, upon the third bleeding, and rose again to 74 and 80 after the third replacement with gelatin. Hematocrits

were 66 to 80 per cent, respectively, and the animals were markedly dyspneic. No erythrocytes were replaced in any of the triple hemorrhage experiments. It appears probable that death of these two dogs was due largely to anoxemia, resulting from a too diastolic reduction in numbers of erythrocytes, rather than to depletion of plasma volume. The contrast between the gelatin and the saline-infused animals was most striking in the response to a third hemorrhage. Only eight to 21 cc per kilogram, with an average of 15 cc, were bled from the saline-infused animals to reduce blood pressure to 30 mm

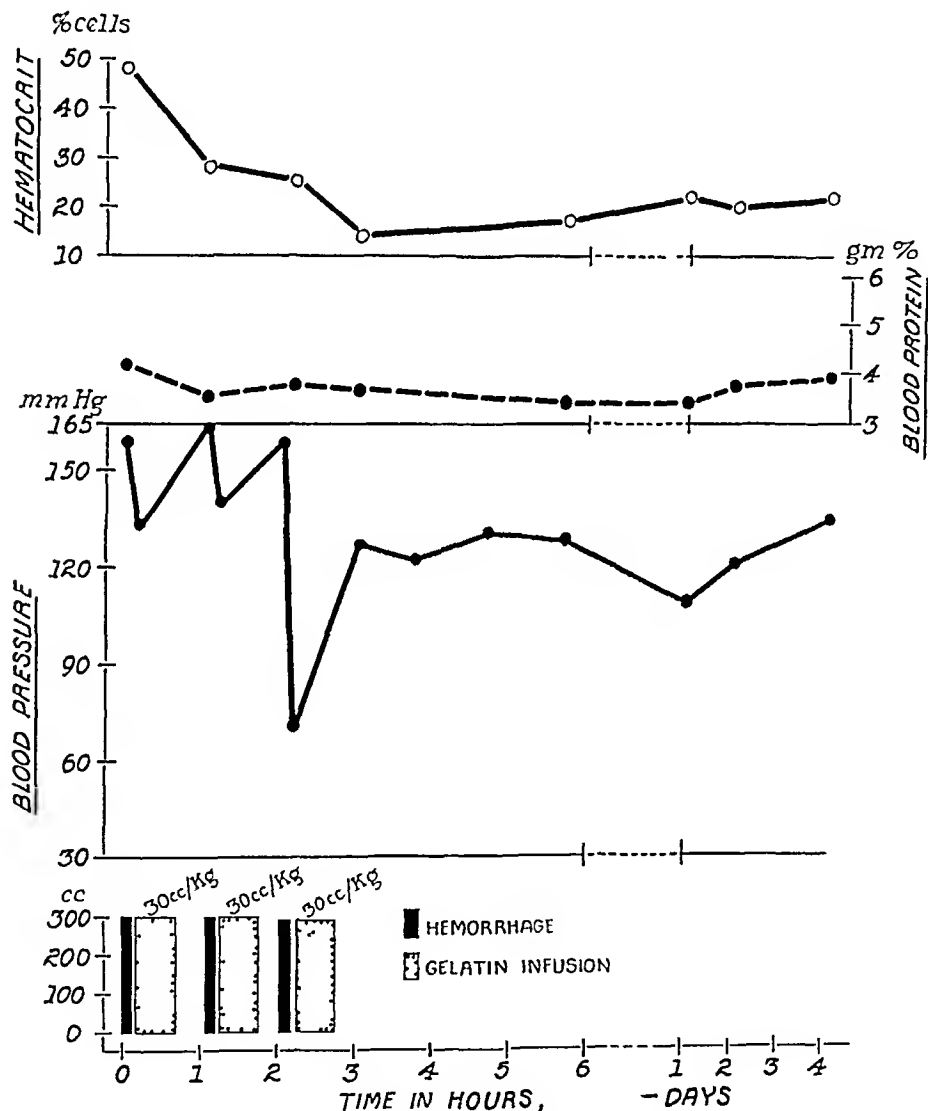


FIG 5—Gelatin in triple hemorrhage

Hg Thirty cubic centimeters per kilogram could be withdrawn during the third hemorrhage from each of the animals infused with gelatin, without reducing blood pressure to such a critical level.

The dog illustrated in Figure 6 showed definite and maintained improvement following gelatin infusions although prior saline infusions had failed to restore stability of the blood pressure. Total protein concentration, hemodilution and blood pressure were increased and well maintained after

each gelatin infusion. Despite a blood pressure of 50 mm of Hg, and below, for several hours during the period of saline infusion, the administration of gelatin was followed by complete recovery.

3—PROLONGED HEMORRHAGE AND SUSTAINED HYPOTENSION

The spontaneous compensation of the dog to hemorrhage, and the effectiveness of fluid replacement are markedly influenced by the rate of bleeding, and the degree and duration of the hypotension^{28, 29, 30, 31, 32}. When the bleeding was prolonged or intermittent, and the blood pressure main-

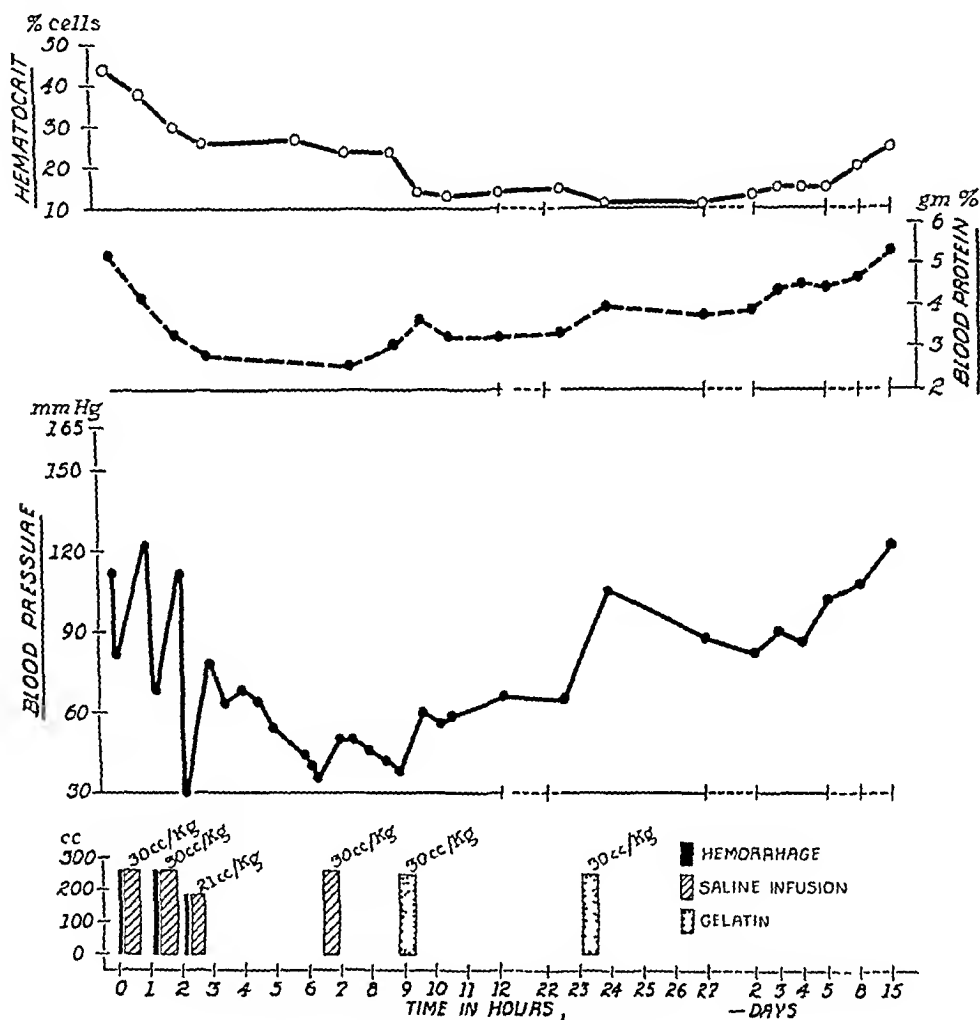


FIG. 6—Saline gelatin in triple hemorrhage

tained at critically low levels by subsequent repeated withdrawals of blood, the response to a replacement of plasma volume is altered and the adequacy of the infusion fluid correspondingly diminished. Although hemodilution and increase in plasma volume and blood pressure occur after infusion of fluids, determining factors apart from blood volume in the blood pressure maintenance, such as peripheral resistance, may not be adequately compensated for by the infusion, and the circulation may fail^{30, 33}.

In the following experiments gelatin as a plasma substitute was studied by comparison with saline and also with plasma under conditions wherein

saline was of little value in the majority of cases, and plasma was uniformly effective

Sixteen dogs, under nembutal anesthesia, were bled in three stages, over a period of 30 to 40 minutes. Mean arterial blood pressure was maintained between 30 and 40 mm Hg for 30 to 40 minutes by additional bleeding if the blood pressure rose above 40. If the blood pressure dropped two

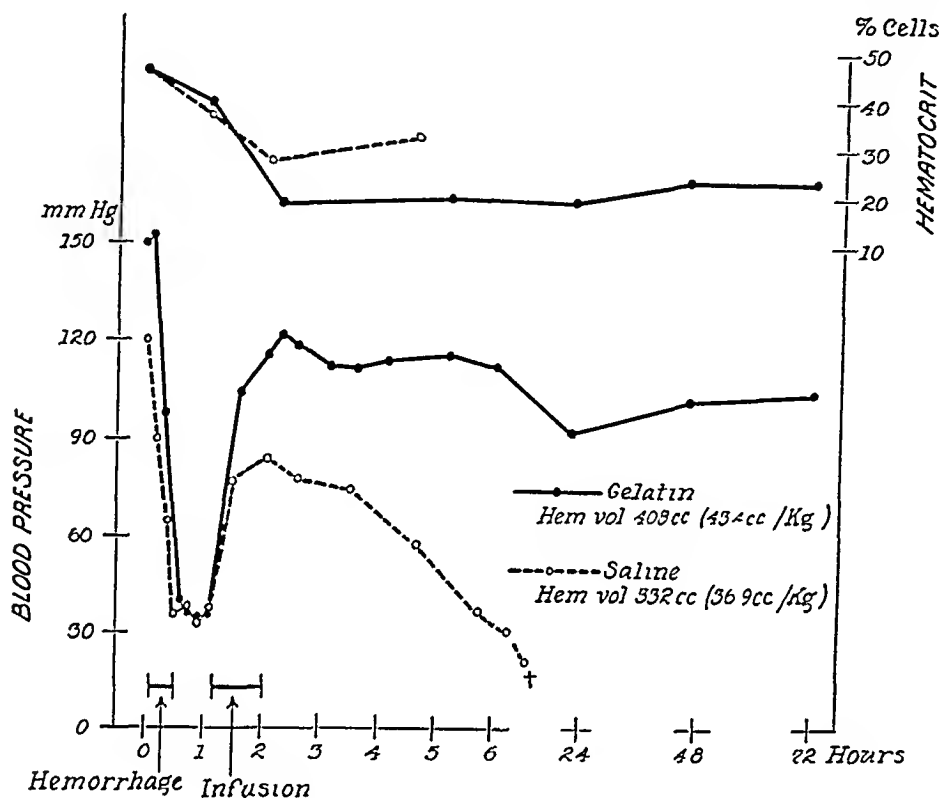


FIG 7—Gelatin and saline in hemorrhage

or three millimeters below 30 mm Hg whole blood was injected in order to maintain the pressure at approximately 35. An infusion volume of the substitute equal to the volume of blood withdrawn (minus the amount replaced in keeping the animal alive during the hypotensive period) was administered at a uniform rate in each case.

Results—Three untreated dogs succumbed within two and one-half hours. Three of five saline-infused dogs died within two to six hours, although the blood pressure after infusion was poorly maintained, two dogs recovered in spite of persistently low blood pressures of between 60 and 80 mm Hg for many hours after infusion. The blood pressure of all five gelatin-infused animals was increased to over 100 mm Hg upon injection of approximately 50 per cent of the infusion volume, it was further increased and well maintained following completion of the infusion (Figure 7). Complete recovery was rapid and uneventful in all five animals.

Three dogs infused with plasma reacted in much the same manner as did the gelatin-infused dogs, and all recovered. Figure 8 is typical of all

plasma and gelatin-treated animals. The hemodilution and increase in plasma volume, as indicated by hemoglobin and hematocrit, was more marked after gelatin infusion than after plasma. This may be due to the fact that the six per cent gelatin preparation used has a colloid osmotic pressure value

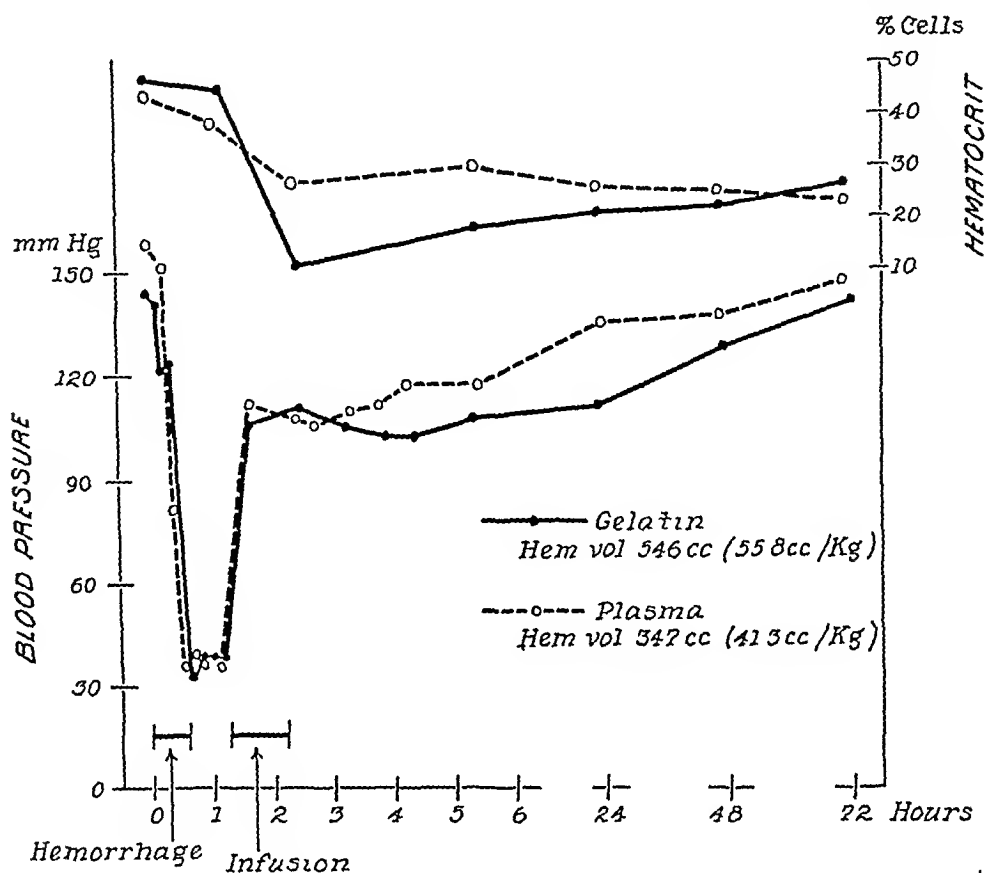


FIG 8—Gelatin and plasma in hemorrhage

greater than that of plasma. Gelatin, under the conditions of this experiment, is undoubtedly superior to saline, and compares favorably with plasma as an effective blood substitute in maintenance of colloid osmotic pressure, blood volume and blood pressure. Gelatin thereby permits complete recovery of animals from a state of posthemorrhagic hypotension, which is fatal to untreated controls and to a majority of saline-infused animals.

DISCUSSION—The question may be asked how gelatin compares with plasma and other plasma substitutes in experimental hemorrhage, under more drastic conditions where even plasma is not uniformly adequate for survival. Experiments now in progress, involving further prolongation of the period of hypotension, tend to indicate that under such extreme conditions the gelatin solution as now constituted falls short of being a complete replacement for plasma. Although the increase in blood volume may be even greater, and may be as well maintained after gelatin as after plasma, the blood pressure is more adequately sustained and survival more definitely assured with plasma than with gelatin. Hemodynamic factors, in addition to replacement of colloid osmotic pressure and plasma volume, enter into a consideration of complete recovery in these experiments.

In general, the results from a rather small number of dogs subjected to experiments on hemorrhage have led us to the tentative conclusion, that gelatin because of its colloid osmotic properties is definitely superior to saline, but may be deficient in some of the beneficial properties of whole blood or plasma. When tested under conditions where replacement of colloid osmotic pressure and plasma volume are sufficient, that is, before the exhibition of the so-called "irreversible" factors described by Wiggers^{10, 13, 14} gelatin compares favorably with plasma.

IV—GELATIN IN BURN SHOCK

Although a given blood substitute may be found to be entirely satisfactory in the treatment of hemorrhage or posthemorrhagic shock it may or may not be equally efficacious in treatment of other shock states, such as those following thermal or mechanical injuries. Ely and Angelo¹³ have concluded from their observations on rabbits subjected to sublethal burns, that a gelatin-glucose-salt solution is as effective as plasma in combatting the hemoconcentration. Grodins¹⁴ recently reported that gelatin-saline is much more effective than saline alone, and about equal to plasma, in producing a sustained rise in blood pressure of dogs in shock resulting from limb trauma.

In studies of gelatin as a plasma substitute in burns, it seemed important to determine the hemodilution, blood pressure and other criteria of colloid osmotic pressure and fluid distribution in the first 12 to 24 hours, and also the later response of the treated animals in the so-called "acute toxemia" phase.

Eight of 30 dogs burned were used in trials to determine, by a controlled reproducible procedure (similar to that described by Tuslei, Egbert and Williams³⁵), the degree of injury which would be fatal to most if not all untreated animals, a burn not so severe as to be irreversible, but one in which plasma therapy might still be effective. The following procedure was used in the 22 dogs included in this report. The hair of the animal was closely clipped from the hindquarters and body, up to the axillae. The animal was anesthetized with morphine and amytal, then immersed up to the axillae in water at 72° C for 60 seconds. Ether was used to supplement the anesthesia during the immersion. Observations were continued to death, or for a period of 72 to 96 hours of survival, at which time the recovering animals were sacrificed for pathologic study. All dogs were infused with 30 cc per kilogram of body weight of the test solutions, at comparable intervals of time (two and nine hours) following the injury. The volume of the third infusion varied between 15 per cent and 30 per cent of body weight, depending upon the extent of the hemoconcentration at the time. Other conditions were kept uniform, including the taking of blood samples and blood pressure determinations. The animals were permitted to recover from the anesthesia. Sulfathiazole ointment was used to control skin infections.

Results—The average survival time of five untreated animals was 11 hours, with a range of from four to 19 hours. Of the five saline-treated animals, two recovered, and were sacrificed at 72 hours, while three succumbed within nine to 20 hours, with an average survival of 13 hours. One gelatin-infused dog recovered, seven died in from nine to 67 hours, with an average survival of 28 hours. Three of the four plasma-treated dogs recovered, one of the plasma animals died at nine hours, just previous to the second infusion.

Although the hemodilution effect of saline was slight in comparison with gelatin or plasma, it appeared that saline alone was beneficial to these animals. Two dogs survived the first 12- to 24-hour period of critical plasma leakage, reached the stage when compensatory blood volume control was reestablished, and hemoconcentration spontaneously disappeared while the blood pressure was maintained.

The rapid progressive hemoconcentration, due essentially to leakage of plasma into the injured area through capillaries permeable to protein, was well compensated by gelatin infusions. Figure 9 is representative of typical cases in each of the four groups of animals. The colloid osmotic pressure of the plasma protein appeared to be adequately replaced by gelatin, since the hematocrit and hemoglobin levels could be brought to normal, and were about as well maintained as with the infusion of equivalent volumes of plasma, as shown by Figure 9 and Table III. The rate of hemoconcentration following the first and second infusions of gelatin, as compared with that following plasma infusion, suggests that the gelatin molecules may be as well retained by permeable capillaries as are the plasma proteins.

Discussion—With gelatin infusions the survival of the animals could be extended beyond the period when plasma loss into the burned area might be considered to be a cardinal factor. Although the hemoconcentration was corrected, the blood pressure was not permanently maintained and, with the

TABLE III
SUMMARY OF AVERAGE VALUES
HEMOCONCENTRATION (HEMATOCRIT) OF DOGS SEVERELY BURNED

Treatment	No of Dogs	Hematocrit (% cells) Normal	Per Cent of Normal			
			Infusion I		Infusion II	
			Before	After	Before	After
Saline	5	44	136	126	153	127
Gelatin	8	42	137	105	145	95
Plasma	4	45	140	116	149	94

exception of one dog, the animals, nevertheless, succumbed. The mechanism involved in this circulatory collapse which is unassociated with hemoconcentration in the secondary phase of burn shock remains obscure. The possibility of functional impairment of some vital organ such as liver, adrenal or kidney,

already damaged through anoxia or through absorption of some hypothetic toxic substance from the burned area, has not been excluded

Since gelatin compensates for the osmotic pressure of lost plasma protein and apparently corrects the plasma volume deficiency of burn shock, we are determining whether or not the efficacy of gelatin in burn treatment may be enhanced through modification of the gelatin solution or its technic of administration, and through the concomitant use of accessory humoral factors

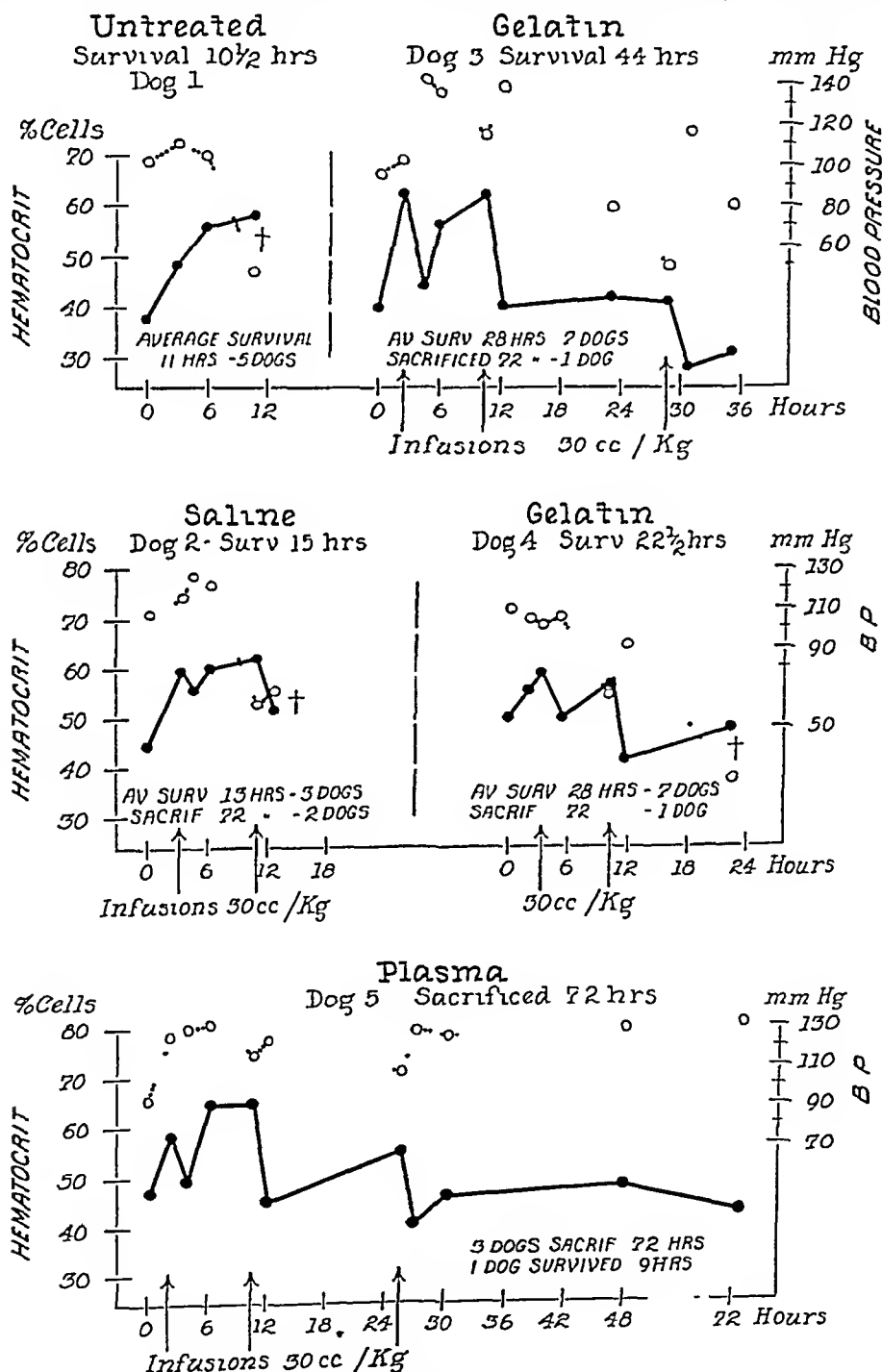


Fig 9—Saline, gelatin and plasma in burn shock

SUMMARY AND CONCLUSIONS

1 Normal dogs tolerate repeated infusions of large volumes of gelatin-saline solution without any serious toxic reactions specific to gelatin. Unfavorable reactions that do occur are reversible and are frequently produced by infusions of comparable amounts of saline or plasma.

2 Pseudo-agglutination of erythrocytes and increase in sedimentation rate, which also occur following infusion of other macromolecular colloids, have been observed both *in vitro* and *in vivo* following infusions of gelatin.

3 Bromsulphalein retention occurred after repeated infusions of gelatin but is present to some extent, in dogs infused with comparable volumes of plasma. Other liver function tests were essentially negative.

4 Kidney function, as determined by urea clearance, was apparently unimpaired after single and repeated infusions of gelatin in normal dogs.

5 Tissue changes observed histologically were reversible and slightly more marked with gelatin than with plasma infused in equivalent volumes and under similar conditions. No chronic tissue storage was observed in animals which received repeated infusions of large volumes of gelatin.

6 A transient diuresis and excretion of gelatin followed its infusion in normal dogs and dogs subjected to preliminary hemorrhage. About half of the gelatin infused was accounted for by urinary excretion.

7 Following massive, rapid hemorrhage and immediate infusion of gelatin, the plasma proteins were apparently replaced at about the same rate as that at which the gelatin protein disappeared from the blood stream.

8 All dogs survived a rapid, massive hemorrhage to point of respiratory failure and blood pressure levels of approximately 20 mm Hg when immediately infused with either saline or gelatin. The higher total protein concentration following gelatin infusion, the considerably greater hemodilution, and the more rapid return of the blood pressure to normal, strongly bear out the superiority of gelatin over saline in experimental hemorrhage of this type.

9 The resistance of the dog to repeated massive hemorrhage, followed by gelatin infusion is markedly increased over that of the animal similarly bled and infused with saline. The saline-infused dog in which the blood pressure continued to decline and remained at critical levels for hours following repeated infusions completely recovered upon subsequent infusions of gelatin.

10 Following a slow, three-stage hemorrhage, with blood pressure maintained at 30 to 40 mm Hg for 30 to 40 minutes, all untreated dogs succumbed within a few hours. Although elevation of plasma volume and blood pressure were not marked or well maintained after infusion of saline, compensation occurred and two of five dogs slowly recovered. Three of the saline-treated animals died in two to six hours. Gelatin infusion resulted in a more marked hemodilution than did plasma infusion under uniform volume replacement. The blood pressure was restored and main-

tained at approximately the same normal levels with gelatin as with plasma, and all dogs made a rapid, complete recovery under these conditions of experimental hemorrhage, gelatin appears to be a suitable substitute for plasma

11 In eight dogs subjected to a standardized reproducible burn of a degree fatal to untreated animals and to a majority of saline-infused animals, gelatin solutions compensated for the loss of plasma from the blood stream, and corrected hemoconcentration to the same degree as did plasma infused in four animals. Although survival was extended in the burn shock gelatin group beyond the period when death occurred in controls presumably from hemoconcentration, seven of eight dogs succumbed after progressive decline in the blood pressure, unassociated with hemoconcentration. Under identical conditions, with plasma infusion only one of four dogs succumbed.

12 If a factor can be identified in plasma which accounts for its ability to maintain blood pressure in the severely burned animal during the secondary phase of so-called "acute toxemia," the addition of this factor to gelatin would probably result in a more adequate plasma substitute for burns.

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DISCUSSION —DR JOHN S LOCKWOOD (Philadelphia, closing) I want to thank Dr Graham for making reference to Hogan's work on gelatin. As a matter of fact, we have referred to it in the manuscript, but because of the shortage of time I omitted reference to it, which I would not have done had I been aware of the fact that that work was done in Cincinnati. Gelatin chemistry has made many advances toward purification and standardization of material, which gives us many advantages over workers of twenty-five years ago.

I also omitted reference in my remarks to the very interesting study being conducted by the group in Chicago, under Dr Brunschwig. We feel that these two studies are supplementing each other in a very useful way. We also believe that gelatin may serve as a means of providing parenteral feeding of protein.

One of the problems we have been up against all along in this work has been to "hew to the line" of studying gelatin as a blood substitute, because so many interesting problems concerning shock and burns have cropped up in connection with the work, that we have been tempted frequently to drop our primary study in pursuit of these possible "will-o'-the-wisps." For example, we think the gelatin work has brought out further evidence of the dissociation of the problem of blood-volume maintenance from the problem of peripheral blood flow in the shocked individual.

The restoration of normal blood volume by the administration of a colloid such as gelatin will not alone constitute adequate therapy in shock.

PROBLEMS OF PROTEIN NUTRITION IN BURNED PATIENTS¹

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FROM THE THORNDIKE MEMORIAL LABORATORY, SECOND AND FOURTH MEDICAL SERVICES (HARVARD), AND THE BURN ASSIGNMENT OF THE SURGICAL SERVICES OF THE BOSTON CITY HOSPITAL AND THE DEPARTMENTS OF MEDICINE AND SURGERY, HARVARD MEDICAL SCHOOL, BOSTON, MASS

ALTHOUGH THE TREATMENT of the burned patient is usually regarded as a surgical problem, numerous underlying physiologic, metabolic and clinical complications must be constantly borne in mind. Frequently, the success or failure of carefully planned and well executed surgical procedures, such as skin grafting, depends upon the early recognition and effective handling of these underlying disturbances. Infection,¹ shock, immediate or late,² anemia,³ and disturbances of kidney or liver function⁴ may occur as complications of burns. All these factors tend to delay healing.

The presence of any, or all, of these factors may also have a profound effect on the metabolism of the patient. An opportunity has been afforded to study some of the abnormalities of metabolism in a large series of burned patients. The details of the earliest of these investigations are given elsewhere.⁵ The present communication deals with only one aspect of this very large problem, namely, the problem of protein metabolism in the burned patient.

Hypoproteinemia occurred frequently in a series of 63 patients upon whom a sufficient number of laboratory observations were made. In some patients, hypoproteinemia was fugitive, and was probably associated with early loss of plasma. In others, it persisted for some time, but was not severe and responded to high protein diets containing from 100 to 125 Gm of protein per day. These diets were supplemented with 25 to 30 Gm of brewers yeast† and other added vitamin supplements,‡ and contained approximately 3000 calories. Other patients did not respond to, or could not ingest, such diets. This group was composed of the most severely burned of all the patients studied, and in them the hypoproteinemia became progressive, and often reached the anasarca level. Simple loss of plasma in the form of persistent surface exudate could not alone account for the hypoproteinemia.

* Presented before the American Surgical Association, Cincinnati, Ohio, May 14, 1943.

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† Provided by the courtesy of the Brewery Foundation, of New York.

‡ Provided by the courtesy of Merck & Co, Rahway, New Jersey.

in these patients. But there is no doubt that this was an important contributing factor, although, unfortunately, one that cannot be studied quantitatively.

A detailed study of nitrogen metabolism has been made upon a patient with a burn of 55 per cent of his body surface. Similar studies have been made upon nine other patients. The data from these patients are not complete but are entirely confirmatory in essential details of the findings reported here. The important laboratory data are presented in Chart 1. All values have been calculated in terms of protein. They include protein intake from all sources.

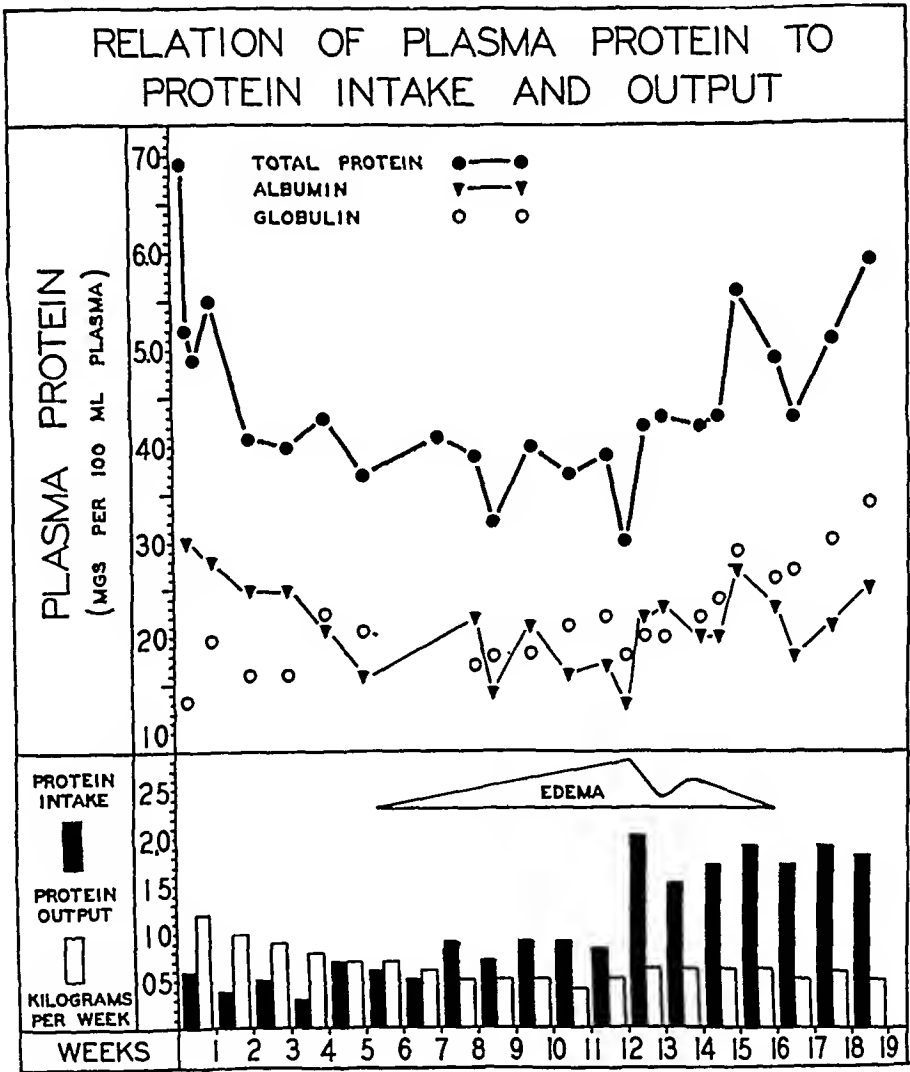


CHART I

CASE REPORT

C J, age 22, a coast guardsman in excellent physical condition and with a non-contributory past history sustained flame burns shortly before entry to the hospital. On admission, a physical examination revealed a well-developed and well-nourished

young man, with burns of such severity that it was later determined that approximately 45 per cent of his body area was involved in third degree burns and a 10 per cent further area with second degree burns. The burns were on the face, scalp, whole back, flanks, and large parts of all four extremities.

His pulse was rapid and thready. He was cold and clammy. His blood pressure was not taken because of his leg and arm burns. Marked hemoconcentration was present and the required 17 units* of plasma were administered based both on the extent of the burn and on hematologic data. The plasma and four liters of saline were administered over a period of 48 hours, all of the plasma being given in the first 24 hours. No debridement was attempted, and his burns were treated by triple dye.

His early complications were hemoglobinemia, hemoglobinuria, with oliguria and azotemia. His azotemia was of a reversible type. The blood nonprotein nitrogen returned to normal after a few days of normal urine output. At the end of 24 hours he was given sulfadiazine by mouth, with satisfactory blood levels and a normal kidney clearance of the drug.

Urine nitrogen data showed the presence of unusually large amounts of nitrogen in the urine, amounting on some occasions to 34 Gm in a 24-hour period. He lost his appetite and, for a period of four weeks, the protein component in his diet did not exceed 80 Gm per day. At the end of six weeks he had sustained a calculable net loss of over 2000 Gm of protein. This deficit was occasioned by the negative nitrogen balance occurring during the first four weeks. These figures obviously do not take into consideration the very considerable loss of nitrogenous material from the burned area which, by clinical observation, persisted for 19 weeks, at which time the skin grafting was nearly complete. Therefore, the nitrogen deficit must actually have been much greater than the calculable 2000 Gm would indicate.

The significance of a protein deficit of 2000 Gm should be carefully examined. It represents an equivalent in terms of plasma of 40,000 ml. Expressed as loss of muscle tissue it represents a loss of ten kilograms or approximately 22 pounds. The problem of balancing such a protein deficit in a severely burned patient by feeding a high protein diet was extremely difficult. By considerable persuasion, the patient was prevailed upon to take many supplementary feedings until his intake was approximately 130 Gm of protein a day, and his caloric intake 3000 Gm. This represented in his case the absolute physical ability of the patient to ingest food by mouth. This diet was continued from the 7th to the 12th week of his hospital stay. From the end of the first week he also had another small source of protein intake in the plasma content of 6000 cc of whole blood transfusions in 12 weeks. These were given in 300-1000 cc doses at frequent intervals. The plasma proteins from this source is included in the values given in the chart. Nevertheless, in spite of cooperation on the part of the patient, and in spite of the fact that an *apparent positive nitrogen balance* was obtained throughout this period of high protein intake, his plasma protein fell and the edema, which became noticeable at the end of the fourth week, progressed. By the beginning of the 12th week the plasma proteins had fallen to 3.1 and the albumin to 1.6 mg per ml of plasma, respectively, and the edema was massive.

His clinical condition at the beginning of the 12th week was desperate and heroic measures of alimentation were begun. Seventy-five Gm of human albumin† and several units of desiccated plasma, reconstituted at ten per cent protein content, were administered and feeding commenced by vein and stomach tube. The details and

* One unit of plasma is 250 ml of therapeutic plasma with a protein content of approximately five per cent.

† Provided through the courtesy of Professor E. J. Cohn.

theoretic discussion of the alimentation used in this patient is given in another communication⁶ Only the essentials of the treatment will be given here The protein intake was increased from 800 Gm to between 1700 and 2000 Gm per week On some days his protein intake amounted to 500 Gm Intravenous alimentation was carried out with amino-acids obtained from acid hydrolysis of casein with added water-soluble vitamins By stomach tube, a high caloric, high protein, high vitamin diet in semifluid form were administered The intubated food was supplemented with 30 to 40 Gm of brewers yeast, 20,000 units of vitamin A, 1000 units of vitamin D, 200 mg of ascorbic acid, 20 mg of thiamin, 10 mg of riboflavin, and 200 mg of nicotinamide per day The nitrogen intake per week administered by vein was equivalent to 225 to 625 Gm of protein, while by intubation over the same period of time from 1000 to 1200 Gm of protein were administered

The results were striking Immediately following the administration of the albumin and concentrated plasma there was an abrupt delivery of the edema, which continued to diminish in degree throughout the first week of high protein intake During the second week of forced alimentation the edema reappeared briefly, due, in part, to an error in making up the amino-acid solution in isotonic saline, instead of in distilled water About 10,000 Ml of saline solution were thus administered over a period of four days before the error was detected However, the correct procedure was reestablished and the edema gradually decreased until, by the beginning of the 15th week, it disappeared The forced alimentation was continued until the end of the 19th week

In the 14th week his general appearance and the appearance of his granulating surface had improved to such an extent that for the first time since the burn it seemed possible to perform skin grafting operations Because of the great area involved, Reverdin grafts were chosen as the only reasonable kind During the next four weeks he underwent, in bed, four three-hour sessions of grafting Novocain anesthesia was used The growth of new skin between the grafts was exceptionally rapid

The total plasma protein rose from the 12th to the 19th week to an almost normal level Following the administration of albumin, there was an abrupt rise in the plasma albumin fraction The loss of edema during the day following the administration of albumin was striking It may also be mentioned that there was a slow rise of globulin from the 12th week on The rise continued and resulted in an abnormally high globulin level The cause of this rise is not at present known Liver function tests at this time were normal although infection was present

At the conclusion of the period of forced alimentation, it was calculated that a positive balance of 6000 Gm of protein existed in this patient However, partition of the blood and urine nitrogen showed no remarkable loss of amino-nitrogen when amino-acids were injected Neither was the total nitrogen of the urine remarkably increased In fact, on one day, when the intake was calculated as 500 Gm of protein, the patient retained approximately 380 Gm and the urine nitrogen excretion showed a 75 per cent conversion of all excreted nitrogen to urea It would appear, therefore, that the loss of nitrogen through the granulating surface or the demand for tissue must have been very great, since, while the calculated nitrogen deficit based on intake and output studies was more than balanced by forced alimentation, he continued to metabolize and to retain large amounts of protein

The clinical improvement of the patient under this regimen was striking In the 19th week he was returned to a diet of 125 Gm of protein without noticeable return of edema In the 23rd week he was weighed for the first time since the accident Although his health and appearance had improved greatly from his worst condition, he was still 55 pounds below his normal 167

DISCUSSION —The findings in this patient, and in the eight other patients studied, are confirmatory of the observations of Lucido.⁷ In severely burned patients there appears to be an excessive loss of nitrogen into the urine in addition to large losses of nitrogen by exudation from the burned surface, and an increased nitrogen demand for the building of new tissue. These three factors can result in serious nitrogen deprivation, with consequent edema and general malnutrition. The causes of increased nitrogen loss are many. Tissue destruction, infection, increased metabolism and demand for protein for the repair process all play a part.

It must be emphasized that, while the majority of burned individuals may restore nitrogen balances on simple dietary regimens, severely burned patients may not. There was a direct relation between the extent and severity of burn and the amount of nitrogen loss in the present series of cases.

Nitrogen balance studies based upon urine and stool analyses, together with known nitrogen intake, cannot reveal the quite considerable nitrogen loss from the burned surface and the demand for building new tissue. On a high protein diet alone, this patient developed a protein deficit of 2000 Gm., based upon intake and output studies, which was eliminated and a final, apparent, positive balance obtained. In spite of this, the patient's edema increased and it was not until a total nitrogen retention estimated at over 6000 Gm. of protein had been obtained that the edema was completely delivered and a good nutrition obtained. In other words, at least 6000 Gm. of protein were required, over and above that indicated by balance studies by this patient, and this only after the net loss of 55 pounds of his original body weight.

These results suggest that an early appraisal of nitrogen losses in burned patients is necessary. When marked negative nitrogen balances appear, steps must be taken to provide an enhanced nitrogen intake. In some severely burned patients positive nitrogen balances will be found impossible to maintain from diets alone, due to the physical impossibility of ingestion of such diets. In such an event, it is suggested that forced alimentation by intubation or by the intravenous administration of amino-acids, with the precautions previously stated,⁷ should be attempted as soon as possible.

With such protein deficits as shown here, replacement by whole blood or plasma transfusions are clearly impossible, since it would be necessary to administer 120 liters of plasma to accomplish the equivalent of the supplementary alimentation given. The only satisfactory way that can be considered at present is forced alimentation by intubation and amino-acid administration by vein with proper precautions.

SUMMARY AND CONCLUSION

1. Increased nitrogen excretion in the urine of some severely burned patients has been established.

2 Calculable nitrogen deficits, based upon intake and output studies alone, of some duration and great magnitude have been observed

3 Correction of such a deficit by high protein feeding failed to bring a patient into true nitrogen balance because of incalculable losses which were probably from the burned and granulating surface

4 Heroic intravenous and tube feeding apparently restored his true protein balance. This feeding reached a level of intake of the equivalent of 2000 Gm of protein per week, and resulted in establishment of an apparent positive nitrogen balance of over 6000 Gm

5 In spite of this apparent positive nitrogen balance, he is still more than one-third below his normal weight, so that even the calculation and considered deficits are much below the actual one

The authors acknowledge the technical assistance of the Laboratory Staff of the Thorndike Memorial Laboratory and of the Burns Assignment. They also express their gratitude to the Surgical Staff and the Special Diet Kitchen of the Boston City Hospital, without whose cooperation this study could not have been made.

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DISCUSSION—DR LELAND S. MCKITTRICK (Boston). Doctor Allen asked me if I would pinch-hit for him. I feel totally inadequate to discuss any one of these three papers. Doctor Allen felt, however, that it might be of some interest, as a part of this discussion, to summarize briefly the results at the Massachusetts General Hospital on the patients from the Coconut Grove disaster. When he found he had to leave town he handed me this slip of paper on which were some figures given to him by Dr. Oliver Cope, who had taken a very active part in all the work of this group of patients.

There were 114 casualties brought to the Massachusetts General Hospital in the period of about an hour and a half. There were a few stragglers after that, but not very many. Fifty-five of those were dead on arrival, and within 15 minutes another 20 died making a total of 75 deaths out of the 114 patients. Thirty-nine patients were admitted for treatment.

The hospital was particularly well suited to handle a group of this size. One surgical floor was completely evacuated, and these 39 patients were promptly sent to this floor.

These burns all followed a pretty uniform pattern—face, hands and trunk were

burned. It was apparently a flash-type of burn, and practically all of them had some type of pulmonary complications. Many of them had pretty severe burns of their upper respiratory tracts. There was little or no burn shock, possibly because of, or in spite of, the fact that it was a cold night, they were all wet, and many of them had been out in the cold for a matter of 20 or 30 minutes before they had arrived at the hospital. There were no associated injuries of any kind, no fractures, no open wounds. It was purely the burn and its associated problems.

Doctor Churchill felt that this should be an ideal group to try a method of treatment which he had come to believe was well suited to burns of this type. There was no debridement. There was no cleaning. A simple boric ointment dressing and pressure were applied to wherever the burns might have been. On the faces, nothing but the nose and mouth were left open. Those who were not sensitive were given tetanus antitoxin. Sodium sulfadiazine was given to all of them. In this connection, it is interesting to note that the bleb fluid contained the same level of diazine as did the blood. The slough of the deep burns contained organisms, but there was no cellulitis, lymphangitis, or lymphadenitis.

It was felt that the isolation of this group of patients was about as complete as could be obtained. Visitors were not allowed. Nobody was allowed on the floor except those actively associated with the care of the patients. Even a lot of men who had spent all night treating burns were not allowed to go in and follow the cases. Everybody who had to do with the patients was masked and, so neat as possible, the strictest aseptic precautions were carried out.

Now as to the results. Of the 39 patients, seven died. Within the first 12 hours, there were no deaths. The seven deaths occurred from 13 to 62 hours—all of pulmonary complications. At the end of 42 days, one of the men committed suicide.

There were seven patients who had from 50 to 70 per cent of their bodies burned, and of those seven, four lived. Nearly all patients had some degree of pulmonary complications, five requiring tracheotomy. Three of these died.

As Doctor Whipple said, and as would be expected, the second degree burns healed very promptly. Seventeen of the 39 patients were discharged from the hospital by the end of two weeks.

Nine of the ten patients with deep burns required extensive skin grafting. All of the patients have now left the hospital.

There were two or three points which are worthy of note. Without any question, we gave some of these people too much morphine. We misunderstood the restlessness and the mania of anoxia for pain, and in two or three occasions morphine was probably given to a hazardous degree. It was the feeling of Doctor Beecher, and, I think of all the group, that the barbiturates, in many instances could have been employed with much greater safety. Care must be taken not to give excessive salt, especially if normal saline is used to dilute the plasma.

After a review of these patients, it was our feeling that, for a group of casualties such as this, the method of treatment employed had certain definite advantages. It was simple, could be easily applied by less skilled personnel, permitted early application, thus minimizing contamination, and did not interfere with the treatment of shock or anoxia. I think we were all impressed with how quickly they became comfortable and how little medication was required to keep them so.

DR. ROBERT ELMAN (St. Louis). The war and other catastrophes often give a ray of light to physicians and investigators, because it stimulates and gives opportunity of learning a good deal more about the various injuries and difficulties with which we are confronted. I think this is important, and Dr. Whipple has emphasized the fact that we are now learning a great deal more about burns than we ever did before. This point should be emphasized because at no time in the treatment of any condition should we ever rest on our laurels and think that the problem is finished.

To anyone who has tried to prepare extensive full-thickness third degree burns for skin grafting, the problem of nutrition is a very real one, and yet it is frequently overlooked. The observations of Dr Lund, and his collaborators, have added much to our knowledge of the mechanism of the nitrogen loss in these severely burned patients, and I hope that their further studies may reveal the cause of this excessive loss, so that it may be prevented. Until this occurs, however, we must treat this nitrogen loss by increasing tremendously the nitrogen intake with high protein feedings. The magnitude of this increase is well shown by the high protein diets given their patients. That they were successful is indicated by the fact that they were able to give one of their patients *in one day* as much as 500 Gm of protein, a nutritional feat which to me could be described as a therapeutic triumph.

It might be mentioned, of course, that an ounce of prevention is often worth a pound of cure, and that if one starts the high protein and high caloric intake as early as possible after the burn, much of the protein deficiency can be prevented. In one of our cases, the kodachrome of which is presented herewith, (taken on the 34th day), we started our high protein diet within the first week after the burn, in fact, as soon as the vomiting stopped. This was more than a 40 per cent full-thickness burn and, as you can see, the granulating area is free of slough and clean. She was treated by rapid coagulation with tannic acid and silver nitrate. I attribute part of her excellent general condition to the fact that she was very fond of chocolate malted milk and ice cream, and this was given her practically day and night. She probably ingested as much as five Gm of protein per kilo per day, although we do not have the exact figures. This does not reach the record established by Dr Lund, which is almost ten Gm of protein per kilo per day.

DR EVARTS A GRAHAM (St Louis, Mo) I have nothing very much to add to the discussion, except that I wonder if Doctor Lockwood is familiar with the work of Doctor Hogan on the use of gelatin, which was published about the year 1912. Doctor Hogan was a pupil of Dr Martin Fisher, who is Professor of Physiology at Cincinnati.

This work was done before blood transfusions had reached a practical stage. It seemed that the promise of gelatin as a medium which could be used in the treatment of shock in place of the impractical blood transfusion at that time, might answer a very difficult problem which confronted surgeons.

The difficulties which confronted Doctor Hogan, however, were, first of all, I think the difficulty in having a gelatin which was nontoxic, but, at any rate, in his experimental animals he got results from the use of gelatin which seem to be very promising indeed.

LT COMDR MAUROT, MC (Norfolk, Va) As one member of the burn team at Norfolk General Hospital, I have helped to treat all the burns received there during the past seven months. We have met with all the problems outlined so excellently by Doctor Lund. During this time, we have tried to combat the hypoproteinemia with plasma, and have been unsuccessful. We also had difficulty in feeding a sufficiently high protein diet to a patient to have their protein reach a point of six to eight per cent.

Doctor Lund spoke of hypoproteinemia and also the terrific anemia seen in these cases. In some cases we have seen a burn case having red blood count of four million fall to two and a half million in four days. We cannot explain this terrific anemia in such a short time. We have not seen any cases of jaundice, nor any cases of hemoglobinuria, and we have not been able to prove, as some writers have stated, that there is an increased fragility of the red blood cells.

There is one point I wish to bring out on skin grafting. We attempt to graft our burns as soon as possible, if feasible, between the tenth and fourteenth day after the initial injury. In some of our cases in which the burned area is more than 50 per cent, it has been difficult to find areas of skin from which to graft, so we have developed the following technic, which, however, is not original, although there is nothing in

the literature upon it. We take a section of skin approximately an inch and a half wide and three inches long, the full-thickness of skin, shave all the fat from the under surface of it, and divide the skin into two portions, giving us two pieces of skin approximately three inches long and approximately three-quarters of an inch wide. We then shave the full-thickness grafts, each of which are about three-quarters of an inch wide and approximately a thirty-second of an inch thick. The donor area is closed by interrupted sutures. From a piece of skin of this size, we can obtain approximately 200 small pinch grafts, and the donor area can be sutured, closed, and held by primary means.

In other grafts that we did originally, using Thiersch's or intermediate-thickness grafts, the donor area will not heal and usually becomes infected, or in other words, you are merely "robbing Peter to pay Paul"—you take skin from the thigh to place on the arm, and then the thigh will not heal and you have to graft it.

DR ALEXANDER BRUNSCHWIG (Chicago) We have been interested in gelatin also from the standpoint of parenteral nitrogenous nutrition. It has been possible to maintain dogs in positive nitrogen balance 12 days or more with daily injections of gelatin, dogs who take little or no protein by mouth. It can be used in man, but the real value of its use in man, of course, has to be determined. There is no question about its safety. We have given it in doses of 100 to 150 cc of ten per cent solution daily for 12 days, supplementing light diet by mouth, without any reactions. As much as 300 cc of a ten per cent solution of gelatin has been given intravenously, in a short time, to patients without reactions. We have given it to patients for periods of four to five days, followed by a rest period of 10 to 12 days, and then resumption of injections, without observing acquired sensitivity.

In contemplating studies with gelatin, one has to choose the source. There are several kinds: there is hog or calfskin gelatin, bone gelatin, and fish swim-bladder gelatin. They are made in various ways by different manufacturers. As they come from the manufacturer, a ten per cent aqueous solution may gel at room temperature, but autoclaving for 45 minutes or an hour affords a solution that will not gel until much lower temperatures are reached (-8°C , or lower).

I think it offers a very interesting substance with which to work. It is not a complete protein, but by supplementing it with the missing amino-acids it may prove to be a very valuable substance for intravenous feeding. It is easily available, very cheap, and very easy to handle.

DR CHARLES C LUND (Boston, closing) The caloric intake is very important in giving a high protein diet. If a high protein diet is given without plenty of carbohydrate, some of the protein has to be used for fuel.

During the period of highest protein intake, when this man turned the corner, his caloric intake was about 6000 calories per day. During fairly long periods of time, the intravenous amino-acids made up about a third of his nitrogen intake. More can be used if the veins will stand it. In fact, complete nitrogen balance in patients, who do not demand as much nitrogen as these patients do, can be achieved by intravenous treatment alone. There are reactions. I think there are reactions with all available kinds of amino-acids at present, but they are not terribly serious.

I disagree with my friend, Dr Koch, about one point, in his final three-point statement of the all-important things in burns. One of the points was the prevention of infection. Now, when you have a burn with deep, extensive, third-degree loss, you are going to get colon bacilli and staphylococci in the area, no matter what treatment. Complete prevention of infection is beyond human capabilities at present. I think Dr Koch will agree with this. Therefore, think about how to treat this inevitable infection. The best program we can offer is to treat the infection indirectly, by supporting the patient so that he can withstand the infection. That is a principle that goes back for ages. Shattuck, for instance, at Massachusetts General Hospital, in 1897, published a paper on "The Increased Feeding of Patients with Typhoid Fever." His results were

not spectacular, but the principle was absolutely sound, and his results did show a definite improvement

I am very much interested in Dr Mauriot's comments, and I hope he will continue his efforts by using the stomach tube. Dr Whipple has suggested the use of a Miller-Abbott tube.

We used to think one could not undertake grafting until the infection was cleaned up in the whole area. We have started recently, putting small Thiersch grafts onto granulation tissue as soon as a small area of it is free of slough, in spite of there being dying foul-smelling slough very closely adjacent to this area. If the patient's nutrition is right, such grafts, completely surrounded by infection, with the help of a little sulfanilamide perhaps, will take.

AMINO-ACIDS, SERUM AND PLASMA IN THE REPLACEMENT THERAPY OF FATAL SHOCK DUE TO REPEATED HEMORRHAGE*

AN EXPERIMENTAL STUDY

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IN PREVIOUS STUDIES from this clinic it was shown^{8, 9, 11} that the amino-acids of hydrolyzed protein are effective as a parenteral method of correcting hypoproteinemia of nutritional origin. In view of the obvious practical advantages of such solutions over plasma, it was natural to try their possible therapeutic value in the acute hypoproteinemia which follows severe hemorrhage. In this communication are described experimental studies on fatal shock produced by repeated hemorrhage, in which replacement of the lost blood by an amino-acid mixture seemed to have a beneficial effect. A preliminary note has already been published¹²

Extensive experiments, of course, have dealt with the production of surgical shock by hemorrhage,^{13, 25} many by members of this Association^{1, 17, 20}. However, in the present experiments the approach has been, to a large extent, biochemical rather than physical or physiologic. This deserves emphasis, inasmuch, as amino-acid mixtures can in no real sense be classed as a blood substitute because they lack the colloidal properties of blood plasma. The value of such injections, if they have value, must depend upon the ability of the body to use amino-acids to synthesize plasma proteins rapidly, or for nutritive or other metabolic purposes. Nevertheless, comparative experiments were carried out with serum and plasma.

Considerable evidence that protein metabolism is a rapid procedure emerges from the important work²² with isotopic nitrogen. Other workers² have recently shown that similarly labeled amino-acids appear in plasma proteins within an hour after injection. These fundamental studies indicate that it is theoretically possible for injected amino-acids to be made into plasma proteins very rapidly, and thus act as an indirect substitute or supplement to plasma. Undoubtedly, the liver is the key organ in this process and we shall have some evidence to show that this is the case.

EXPERIMENTAL PROCEDURES

Because surgical shock involves so many variables, we adopted a method which seemed to give a relatively uniform response. Instead of basing our experiments on the level of hypotension or the amount of hemorrhage, we subjected dogs to uniform repeated bleedings (10 cc per kilogram of body weight each hour) until death ensued, and then used the survival time as the basis for measuring the effect of various replacement procedures. Systolic

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blood pressure as well as hematocrit and fractional plasma proteins were also determined. General anesthesia was not used. The effect of changes in posture was avoided by carrying out the entire experiment while the animal was in the supine position.

Unselected mongrel dogs, varying in weight from 7 to 19 kilograms, were given water *ad libitum*, but no food during the 18 hours preceding the beginning of each experiment. A cannula was inserted into the femoral artery and bleeding carried out as rapidly as possible, the calculated amount usually being obtained within a minute or two. The systolic blood pressure was recorded before and after each hemorrhage with a Tycos manometer⁷ connected to the same cannula used for bleeding. For hematocrit and fractional plasma protein determinations, samples of heparinized venous blood were taken immediately preceding each hemorrhage. The former was measured after centrifugalization at 3000 R P M for 30 minutes. Supernatant plasma was drawn off, the nonprotein nitrogen estimated by nesslerization, fractionation carried out,⁴ and nitrogen determined by a Kjeldahl procedure.²³

The therapeutic value of the various solutions tested was compared by using them to replace the blood removed after each hemorrhage. The fluids for replacement were sterile, but no attempt at complete asepsis was made during the experiment because of its short duration. The injections were rapid and followed immediately each bleeding, the volume being exactly equal to the volume of blood removed. In most experiments the fluids were injected into the femoral artery through the same cannula used for bleeding, but in a few groups the fluid was introduced into the adjacent femoral vein.

Seven groups of experiments were carried out as follows:

TABLE I

	No. of Dogs	Replacement Fluid
Group I	10	None
Group II	20	10% glucose in normal saline solution
Group III	6	Pure amino acids 5% glucose in normal saline 5%
Group IV	20	Protein hydrolysate 5% glucose in normal saline 5%
Group V	10	Dog serum diluted with an equal quantity of 10% glucose in normal saline
Group VI	10	Citrated dog plasma diluted with an equal quantity of 10% glucose in normal saline
Group VII	10	Heparinized dog plasma diluted with an equal quantity of 10% glucose in normal saline

The protein hydrolysate* was an enzymatic digest of casein (Amigen) or beef serum. No difference was observed in the results with these two hydrolysates. The pure amino-acids† consisted entirely of essential amino-acids.²¹ Both solutions were neutralized with sodium hydroxide to a p_H of 6.5 to 7.5. The nitrogen content of the two was similar, *i.e.*, 0.66 and 0.63 gm per cent, respectively. Serum was obtained by centrifuging clotted dog blood, in some cases it was fresh and in others it had been stored for two weeks at freezing temperatures before separation, no obvious difference was

* Supplied through the courtesy of Dr. Warren M. Cox, of Mead Johnson and Co.

† Supplied through the courtesy of Dr. D. F. Robertson, of Merck and Co.

observed in the effects of these two methods of preparation. The citrated plasma contained about 0.6 gm per cent of sodium citrate. To obtain the heparinized plasma one-half cubic centimeter of heparin solution (Lederle) was added to each 1000 cc of whole dog blood.

It should be pointed out that dilution of whole plasma and serum was necessary, so that the actual amount of plasma protein replaced was roughly the same as that removed. An equal amount of diluting fluid was used because the average red cell volume was 50 per cent. Constancy of the plasma proteins was insured by using pooled plasma from many dogs.

At the termination of each experiment a microscopic section was made of the liver. In a separate series of six dogs, a biopsy of the liver was removed under nembutal anesthesia two hours before the initial bleeding and at death. In three of them glucose was used as replacement, and in the other three hydrolyzed protein.

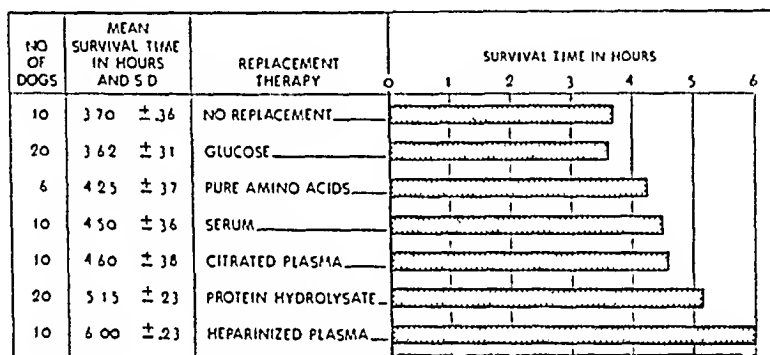


FIG. 1.—Survival Times in the Seven Groups of Experiments Described in the Text. S. D. = Standard deviation, calculated according to usual statistical formulae. Note that replacement with heparinized plasma and a protein hydrolysate gave the longest survival time, and the relatively poor showing with serum and citrated plasma.

EXPERIMENTAL RESULTS

The first observation of interest was that removal by repeated bleedings of an average of but 43 cc per kilo of blood led to an invariably fatal outcome, by contrast, survival is frequent when the same amount of blood is removed in a single hemorrhage. This has been the experience of other observers and we have performed single hemorrhages of this magnitude with a mortality of but 20 per cent.⁹ Clinical observations are similar, in that patients often survive a single bleeding, but are apt to succumb after subsequent though smaller ones. This is especially true of war wounds, for even if there has only been a single initial hemorrhage, further bleeding is sure to occur during débridement.

Survival Time—Of greater importance was the observation (Fig. 1) that replacement with 10 per cent glucose in normal physiologic saline had no influence on the survival time, in contrast to the results with the solution containing hydrolyzed protein, in which the survival time was

5.1 hours, as compared with 3.6 hours for the controls.* The experiments with pure amino-acids were only six in number, but the results (survival time = 4.2 hours) were only somewhat better than with glucose (survival time = 3.6 hours), indicating that the greater effect of the hydrolyzed protein on survival time could not have been due to the mere presence of amino-acids *per se*.

Of special significance were the comparable experiments in which serum, citrated plasma and heparinized plasma were used for replacement. The first two fluids produced no greater survival time than was obtained with the

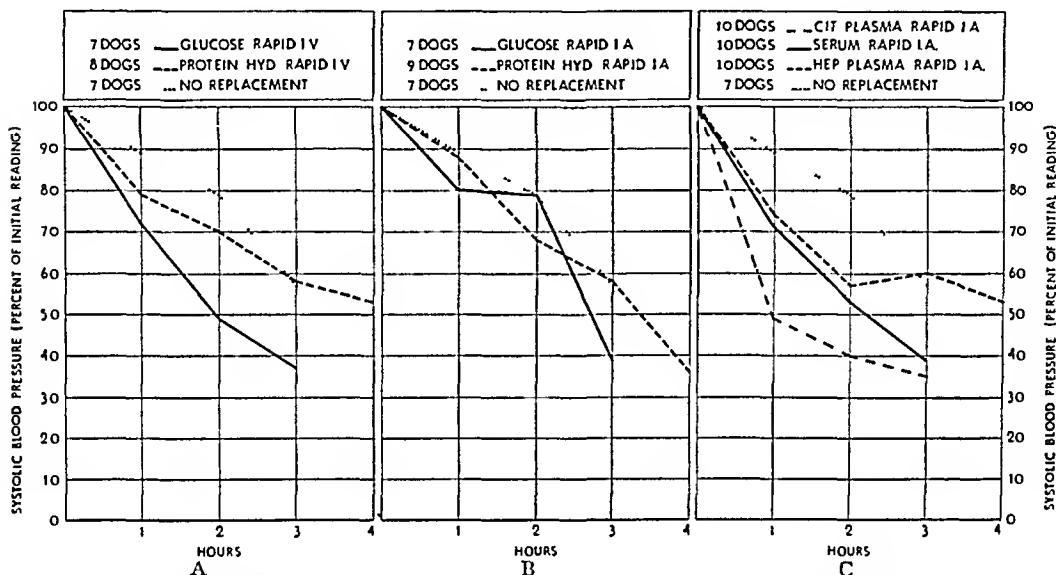


FIG 2—Blood Pressure Response. The curves were drawn from mean values in groups of dogs surviving at least three or four hours but does not include the terminal fall. The curve in which there was no replacement is shown in all of the above three graphs.

A Note pronounced fall during intravenous replacement with glucose as compared with hydrolyzed protein.

B With intra-arterial replacement the difference noted in A is the same, but not as pronounced.

C Note the precipitate early fall with citrated plasma. Serum showed the same though somewhat delayed drop. Heparinized plasma, after two hours maintained a good level of pressure.

hydrolyzed protein. The heparinized plasma, on the other hand, resulted in the longest survival time (six hours).

Of some interest is the fact that no differences were observed in the survival time between experiments in which the fluid was replaced intravenously as compared with those in which they were injected intra-arterially. This topic has been the subject of previous investigations^{6, 15, 16}.

Blood Pressure Response—A progressive fall in blood pressure was observed in each group of experiments as shown in Figure 2. In general, the behavior of the blood pressure was somewhat variable, an observation made by others. In many instances the drop after each hemorrhage was pronounced but recovery good, whereas, in others the blood pressure was

* That this difference is statistically significant is shown by dividing the difference of the means by the standard deviation of the difference. When the figure thus obtained is used in consulting statistical tables, it becomes a certainty that this difference is not a chance phenomenon.

maintained rather well but then dropped abruptly before death. Nevertheless, the average values obtained in similar groups of experiments show significant variations which in most instances can be correlated with the survival time. For example, the greatest blood pressure drop was exhibited by the dogs in which citrated plasma was used, whereas, with the heparinized plasma the blood pressure was sustained after a drop in the first two hours. Moreover, the hydrolyzed protein was followed by a definitely higher blood pressure than similar experiments with ten per cent glucose, particularly when replacement was intravenous rather than intra-arterial. Quite surprising was the fairly good blood pressure, until the terminal fall, in dogs bled with no replacement.

Red Cell Volume and Plasma Proteins—A progressive fall in red cell volume, plasma albumin, and globulin was observed in all experiments, although there were definite and significant differences between the different groups. For purposes of simplification, presentation of this data is limited to that shown in Table II. Therein are figures representing the observations made three hours after the beginning of the experiment, *i e*, after each animal had lost 30 cc per kilo, and just before the fourth hemorrhage was carried out. The numbers refer to the fall in value expressed as a percentage of the initial determination. For example, the experiments in which pure amino-acids were used for replacement at three hours showed a drop in hematocrit to 98 per cent, in albumin to 83 per cent and globulin to 88 per cent of the initial value.

TABLE II

	Hematocrit	Albumin	Globulin
Pure amino acids	98	83	88
No replacement	94	90	94
Hydrolyzed protein	88	81	75
Glucose	83	74	71
Heparinized plasma	79	83	81
Citrated plasma	75	77	79
Serum	85	85	94

The importance of this data on plasma proteins and red cell volume lies in the fact that they measure the factors influencing fluid shift and colloidal osmotic pressure, which, as discussed in a previous paper,⁹ control these compensatory mechanisms following hemorrhage. In other words, restoration of blood volume from extracellular fluid (hemodilution) is indicated by the fall in the hematocrit, while the addition of the two plasma proteins to this diluting fluid, particularly albumin, which contributes 85 per cent of the colloidal osmotic pressure of the blood, is indicated by the comparative changes in their relative concentrations.

Pathology—At autopsy, the bloodless condition of the tissues was a uniform finding. The viscera were pale and in no instance was any engorgement or congestion of the intestines observed. Study of microscopic sections of the liver were of greatest interest and showed in general a shrinking or diminution of stainable cytoplasm. This was less pronounced in the dogs

receiving hydrolyzed protein as compared with those getting glucose as replacement (Figs 4, 5 and 6) The significance of these findings is discussed later on

FIG 3

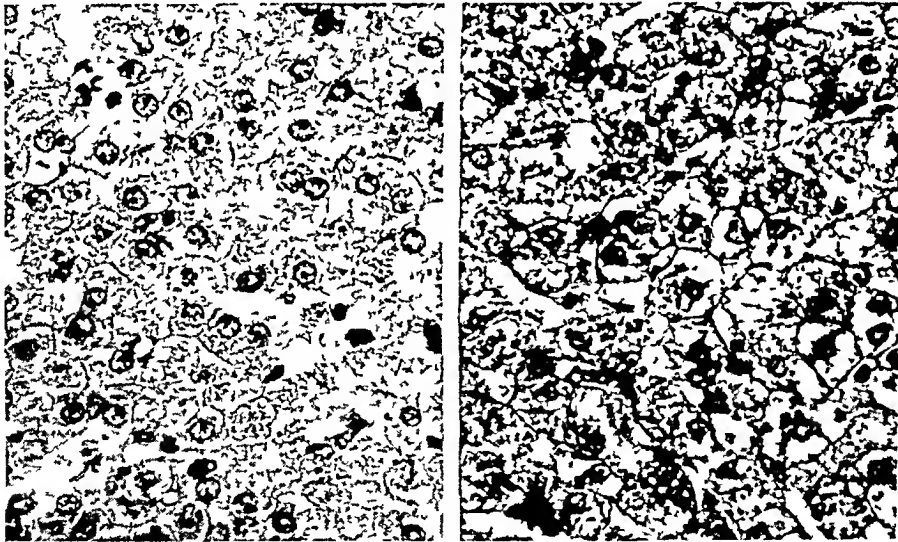
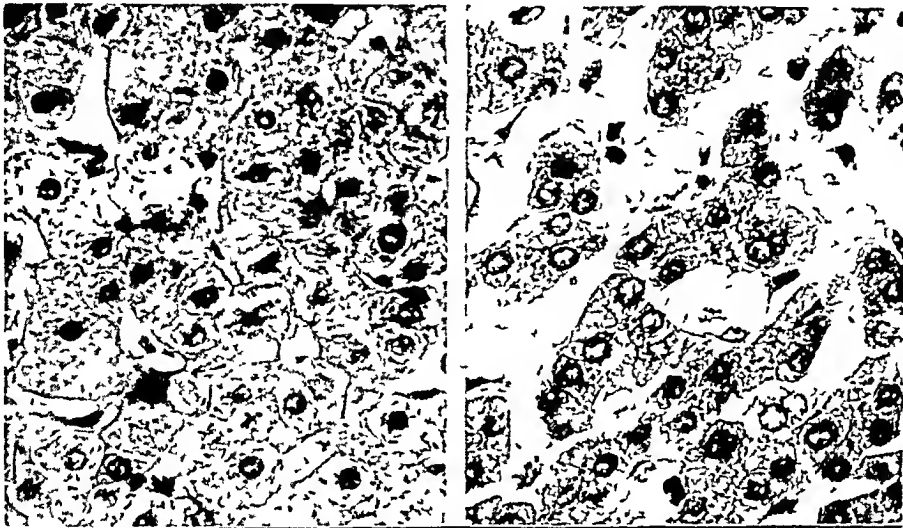


FIG 4

FIG 3—Photomicrographs ($\times 570$) before and after a severe hemorrhage. The patient was a 14 year old female a splenectomy carried out. The section at the left shows the condition of the liver as revealed in a biopsy taken at this time. The section at the right is the autopsy specimen removed 6 hours later, death being due to a large intra abdominal hemorrhage. Note the atrophy the liver cords on the right indicating a depletion of hepatic cytoplasm. The sinusoids are correspondingly dilated.

FIG 4—Photomicrographs ($\times 570$) of liver sections obtained at autopsy in fatal experimental hemorrhages in dogs. In the left the bled blood had been replaced by a solution containing hydrolyzed protein, on the right by glucose. Note the loss of stainable hepatic cytoplasm (vacuolization) on the right as compared with the relatively normal liver cords on the left.

COMMENT—Two features of the present experiments should be emphasized. First, general anesthesia was not used, thus, as pointed out previously,⁹ eliminating certain complicating factors in the normal response to hemorrhage. Second, a fatal outcome was invariable in each experiment without altering the details of the procedure, thus avoiding any subjective influence on observations.

The results with serum and plasma replacement have an immediate practical bearing on the use of these fluids in the treatment of human surgical shock. The poor showing of citrated as compared with heparinized plasma is obvious on comparing the blood pressure response as well as the survival time. This confirms experiments performed by others^{3, 14}. The fact that citrated plasma produced changes in red cell volume and in plasma proteins which were similar to those with heparinized plasma (Table II) suggests that citrated plasma was just as effective in controlling fluid shifts and colloidal osmotic pressure. It would seem, therefore, that a toxic effect of sodium citrate may have been responsible. That serum was no better than citrated plasma is more difficult to explain, although there is some evidence that serum, under certain conditions at least, is toxic when used instead of plasma¹⁹. Serum, moreover, behaved unlike plasma in that the changes in hematocrit and plasma protein were somewhat different as indicated by the findings in Table II. For example, the albumin fell more than the globulin, suggesting some loss of this fraction from the circulation. In experiments by others,¹⁴ serum was also found to be inferior to heparinized plasma, in replacement of large single hemorrhages in the dog. Further study of the effect of serum injections seems necessary.

As to the beneficial effects of hydrolyzed protein on survival time and on blood pressure, the most obvious explanation is that they were utilized in the synthesis of serum albumin, thus enabling the body to withstand the effects of further hemorrhages. Study of the hematocrit and plasma protein determinations does seem to justify such an inference. Thus, perusal of Table II shows a slight but definite difference in the behavior of albumin and globulin. It will be noted that the fall in albumin was relatively less (as compared with the globulin) in the experiments in which hydrolyzed protein as compared with those in which glucose was injected. This suggests that more albumin was added to the diluting fluid in the experiments in which hydrolyzed protein was used.

A contrasting result on red cell volume and plasma proteins is apparent in the experiments in which pure amino-acids were used and the ones in which no replacement was carried out. In both of these groups there was very little hemodilution, which means but slight restoration of blood volume. For this reason, the relatively slight fall in protein was of little significance as far as restoration of lost plasma proteins is concerned. Yet the albumin dropped much more than the globulin, indicating loss rather than addition of albumin to the circulating blood during the rather insignificant inflow of fluid. In other words, the compensatory mechanisms controlling fluid shifts seemed less active than in the other experiments. Why the pure amino-acids proved less effective than the hydrolyzed protein is probably due to the fact that they differed significantly in composition from the latter in that they contained no polypeptides and only the essential amino-acids, most of which were synthetic and, therefore, available only as racemic mixtures. Because of the last factor, a majority of the amino-acids were present in the unnatural form, which are probably biologically ineffective.

In evaluating the results with hydrolyzed protein, the biopsy studies of the liver are of considerable interest. In general, they show changes indicating that the liver contained a higher protein content in the experiments with

FIG 5

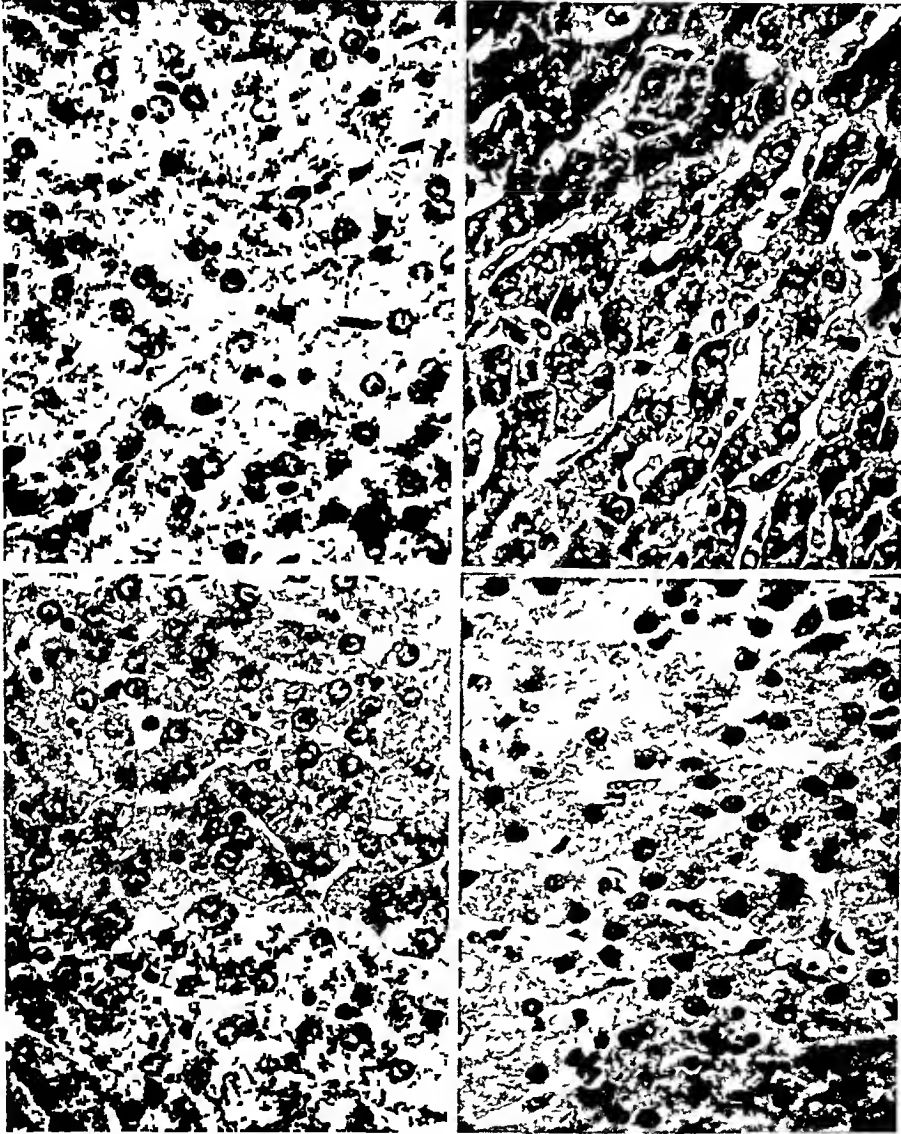


FIG 6

FIG 5—Photomicrographs ($\times 570$) of liver sections before and after repeated hemorrhages, replacement with glucose. This experiment differs from the others in that nembutal anesthesia had to be given to get the control biopsy. Nevertheless note the atrophy of the liver cords as well as vacuolization of the cytoplasm on the right as compared with the control on the left. This change is to be contrasted with Text Fig 6 in which hydrolyzed protein was used for replacement.

FIG 6—Photomicrographs ($\times 570$) of liver sections before and after repeated hemorrhage, replacement with solution containing hydrolyzed protein. Note the relative absence of atrophy and vacuolization on the right as compared with the changes observed in Text Fig 5.

hydrolyzed protein than in those with glucose (Figs 5 and 6). This interpretation is based upon many previous studies in which the amount of protein in the liver seemed to be correlated with the stainable protoplasm.^{10 11} Corroborative, are other observations¹⁸ in which stained droplets in the liver

apparently protein in nature, disappeared following experimental hemorrhage. Moreover, we have observed, in a human, what seems to be a loss of hepatic cytoplasm as a result of a fatal hemorrhage (Fig. 4). Further studies, however, will be necessary before this correlation rests on more secure foundations.

That the speed of the intravenous injection has some influence on the results also seems evident. Thus, many of the experiments described herein were repeated, giving the replacement fluid slowly by intravenous drip over the course of the hour between hemorrhages instead of rapidly following each bleeding. The results were remarkably similar to those reported above, with the exception of glucose and heparinized plasma, which resulted in a slightly longer mean survival time when given slowly intravenously. That the manner of replacement has an important influence was also noted in a report²⁴ of shock induced in dogs by the tourniquet method, while fatalities were successfully combated by repeated small plasma transfusions, the slow injection of plasma for 30 to 50 minutes following release of the tourniquet resulted in shock and death, although the total amount of plasma given to the two groups was the same. Reasons for this difference were not found on analysis of the data on hematocrit, plasma protein, hemoglobin and blood volume.

A comment should be made in regard to amino-acid mixtures made by hydrolyzing protein, *i e*, any protein may be hydrolyzed to any degree. The product used herein was hydrolyzed to about 70 per cent of completion, in other words, 30 per cent of the protein molecule was still in the form of amino-acid aggregates or small polypeptides. The larger these aggregates the more they approach the properties of protein and the more likely they are to possess colloidal properties. These considerations may eventually prove of practical importance, inasmuch as slightly hydrolyzed proteins may be of sufficient molecular size to exhibit the properties of plasma proteins and yet may have lost any anaphylactic or antigenic properties possessed by the intact molecule. Moreover, no one knows how small the hydrolyzed protein molecule must be before it can be utilized as such by the body in the synthesis of other proteins or for other metabolic needs. Further investigation would seem to be worth while.

Certain additional clinical implications may be drawn from the present data. Hemorrhage, in many instances, will be accompanied by considerable trauma. Whether this be the result of an accident or a planned operative procedure, there is an increased nitrogen loss indicating excessive tissue protein breakdown⁵. When there is acute loss of protein, as in hemorrhage, the body stores will attempt to replenish this loss at their own expense, thus adding to the depletion of tissue protein. To replace protein lost from the circulating blood is a simple problem and can be accomplished directly with whole blood or plasma. On the other hand, correction of tissue protein depletion is easier and more direct with amino-acids than with plasma, even when large amounts of the latter are given. Thus, in the severely wounded or severely depleted individual nitrogen metabolism can be restored to normal more readily by using protein hydrolysates, thus, accelerating recovery. Moreover, if whole

blood or plasma is not available it would seem that protein hydrolysate is preferable to the use of ordinary crystalloid in the treatment of shock due to hemorrhage

SUMMARY

Fatal surgical shock in unanesthetized dogs followed bleeding ten cubic centimeters per kilo of body weight, every hour, the mean survival time being 3.6 hours. There was a progressive fall in blood pressure, in red cell volume, and in plasma albumin and globulin in all experiments. If the blood removed each time was immediately replaced by the same volume of various solutions, significant differences were observed as follows:

The survival time was unchanged with glucose in saline, increased to 4.2 hours with pure amino-acids, to 5.15 with hydrolyzed protein. With citrated plasma or serum survival time was but 4.5 and 4.6 hours, whereas with heparinized plasma it was 6.0 hours.

The fall in blood pressure was greater with citrated plasma and serum than with heparinized plasma, whereas, hydrolyzed protein produced less hypotension than glucose.

Study of the changes in red cell volume and in plasma proteins gives some indication that the amino-acids of hydrolyzed protein were converted into plasma albumin. Histologic study of the liver suggests that protein is lost from the hepatic cytoplasm in hemorrhage, and that injecting hydrolyzed protein replenishes this loss, as compared with experiments in which glucose was used.

It may be inferred that in shock due to repeated hemorrhage a solution containing the amino-acids and peptides of hydrolyzed protein has a beneficial influence as compared with glucose and that heparinized is far superior to citrated plasma. Various implications of the problem of shock from repeated hemorrhage are discussed.

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DISCUSSION—Dr Robert Elman (St Louis, Mo) The general phenomenon of plasma protein regeneration, particularly by dietary means, has, of course, been extensively studied, especially by the Rochester School, under Doctors George Whipple and S C Madden What we have shown, I believe, is that this regeneration occurs rapidly enough after repeated acute blood loss to have a beneficial effect, provided a proper mixture of amino-acids is injected Such solutions may, therefore, have a place in the treatment of shock, insofar, as they can be transformed into plasma proteins, thus enabling the body to withstand further loss of blood, which might otherwise prove fatal This may at least spare the need for much of the plasma which would be required after the initial hemorrhage

I would like to pursue the biochemical point of view a little further It seems clear that much of the problem in the treatment of shock following hemorrhage concerns the need for rapid restoration of plasma proteins lost in the bleeding Now plenty of fluid is available in the body to restore blood volume spontaneously, actually about 20 liters are normally present in the extracellular spaces of an average-sized adult, and it is quickly mobilized after hemorrhage Unfortunately, however, this fluid contains practically no protein and this is the reason why its compensatory effect is inadequate True enough, plasma proteins are regenerated eventually, but without outside aid, this requires days instead of hours Now, if a soldier dies after a total loss of two liters of blood, one could explain the fatality by saying that the patient urgently needed 60 gm of plasma protein, and that the inability of the body to supply it may be described by a well known phrase—"too little and too late" Yet, consider how strange this is Sixty gm of protein needed in the blood stream, while kilograms of tissue protein are present everywhere, without being used Well might one quote the words of the Ancient Mariner "Water, water everywhere, nor any drop to drink" According to this line of reasoning experimental studies aiming to find means to supplement or supplant the use of plasma might well be directed toward the possibility of accelerating endogenous plasma protein replacement Indeed, it may not be too farfetched to look forward to such acceleration from the tremendous tissue protein stores by merely injecting appropriate enzymes or catalysts

DR LESTER R DRAGSTEDT (Chicago) This paper by Doctors Elman and Lischer presents a number of interesting and puzzling facts I should have anticipated that a single massive hemorrhage would be more apt to be fatal than the gradual loss of the same amount of blood because of the time for the compensatory mechanism to become active in the former case I should like to know if the authors have any explanation for this contrary finding

The better results from the use of protein hydrolysates as compared with glucose, it seems to me is very likely to be explained as they have suggested, by the formation of plasma proteins from the amino-acids supplied It means a much more rapid manufacture of proteins from amino-acids than I would have believed possible

I wonder if a possible explanation could be that in the presence of this massive hemorrhage protein reserves have been called out from the tissues and that the amino-acids supplied have furnished material for the more gradual replenishment of the tissue proteins

The superiority of heparinized plasma as compared with citrated plasma I think is of great and practical importance, now that large transfusions are being administered. It seems likely to me that it can be explained on the basis of the toxicity of citrate.

In a recent experience in our clinic, a very large amount of citrated blood was given a patient upon whom I had performed a total colectomy for chronic ulcerative colitis. The patient was a young man. He died on the fifth postoperative day from a cerebral thrombosis. No studies were made of the coagulability of the blood in this patient, but I have since speculated on the possibility that the large amount of citrate given may have increased the coagulability of the blood to a dangerous degree.

This paradoxical effect of citrate *in vivo* was noted by the early workers on blood transfusion, and I believe they called attention to its possible danger.

I should like to ask the authors if they observed any evidence of intravascular coagulation when they gave these large amounts of citrated plasma?

DR CHARLES C LUND (Boston) This strikes me as a very important piece of work, and I agree with Dr Dragstedt that the findings are not exactly what one would have predicted, particularly in this matter of repeated hemorrhage being more serious than the single hemorrhage.

My experience with amino-acid therapy is very recent and is connected with burns rather than with hemorrhage.

If the action of amino-acids in helping to regenerate tissue—that is, regenerate plasma protein—is as rapid as is shown here, which means a matter of hours rather than of days, it may be possible to replace some of the large amounts of human plasma that are used in treating burns by amino-acids. That will be a very important thing in many ways.

In a hospital such as the Boston City, and others that I know about, that have fair numbers of patients coming in with burns, the burn cases are the ones that tend to keep or to produce insolvency in blood banks. Many burn patients, of course, in spite of large amounts of plasma die. Many burn patients have few or no friends, and it is not at all unusual to use up ten or fifteen or twenty units of plasma on a burn case and not have any of them returned to the bank.

Of course, Dr Elman's experiment has not been carried over from hemorrhage shock into burn shock, but it would seem logical that it might work in burn shock, and would solve this and probably a great many other problems connected with the treatment of burns, shock, and hemorrhage, perhaps in a fairly short time. Although at present the supply of available injectable amino-acids is so short that it is more difficult to get hold of them than it is to obtain plasma, the time may come when we will not have to bleed quite so many million people for plasma supplies, by using amino-acids produced in factories from milk or, as time goes on, other sources of protein.

DR CARL E LISCHER (St Louis, closing) The answer to Dr Dragstedt's question, as to why the repeated hemorrhage of the same amount is more fatal than a single hemorrhage, we do not know, although it seems to us at times that possibly the repeated injury to the vasomotor system is a factor. After a single hemorrhage the organism is allowed to recover without any further interference, if he does recover, but when you bleed the dog repeatedly, although the total amount is the same, each time he gets into the recovery phase you hit him again. I do not know whether that has anything to do with it or not, but it might.

As far as the difference in clotting in these dogs, there was a vast difference between the dogs that received citrated plasma and those that received heparinized plasma. With those receiving heparinized plasma, it was like turning on a water spigot. With those receiving citrated plasma, after two or three hemorrhages it became difficult at times to get the blood to flow freely, and frequently there were clots and the cannula had to be removed and cleaned before the hemorrhage could be obtained.

In regard to the tissue regeneration or the regeneration of proteins, there has been some work indicating that the amount of protein for example in the liver can be correlated with the stainable cytoplasm. This is more of an idea than an established

fact, because it requires more study, and it is a study in itself, but the liver sections of the dogs that received the protein hydrolysates were, on the whole, better than those getting glucose, as far as stainable cytoplasm is concerned

Doctor Lund brought up an interesting point in relation to burns. We have tried amino-acids in burn shock in dogs, without any immediate benefit apparently, but we do feel that if the original or initial shock in burns is controlled by replacement therapy with plasma, that the amino-acids are at the present time, even without further work, very valuable in helping to return that patient to a state of normal metabolism during the convalescence and, thus, will greatly accelerate the convalescence while he is losing so much nitrogen, for so many days, following a burn

TRAUMATIC SHOCK¹

AN EXPERIMENTAL STUDY INCLUDING EVIDENCE AGAINST
THE CAPILLARY LEAKAGE HYPOTHESIS

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TRAUMATIC SHOCK is a state of vascular collapse which develops under such a wide variety of circumstances that some observers regard this condition as divisible into various types according to the etiologic agent involved. Thus, some of the clinical manifestations of burn shock are not seen in the shock of coronary thrombosis or of overwhelming infection. There is, indeed, some discrepancy in the objective findings in the blood chemistry, the hemodynamics, the intra- *versus* extravascular fluid and electrolyte balance, and in the therapeutic response to drugs and fluids. Moreover, there is no unanimity even in respect to the morbid anatomy of traumatic shock, for while one observer adduces evidence of wet or hemorrhagic tissues, another will describe a dry, ischemic state of the tissues.

It is, nevertheless, possible to find common agreement on certain basic issues. When traumatic shock, regardless of cause, exists, it is now agreed that (1) the cardiac output is greatly diminished, (2) the velocity of flow through the peripheral vascular bed is reduced, (3) acid metabolites are present in increased concentration in the blood, (4) the blood carbon dioxide concentration is usually diminished, (5) the venous oxygen concentration is much reduced, while the arterial oxygen concentration may be normal or slightly reduced, (6) the volume of venous return to the heart is reduced, and (7) the blood pressure eventually falls. These phenomena are all invariably present in any and all types, if there are types, of traumatic shock. The focal point of the functional disturbance is in the peripheral vascular bed. It is, therefore, not surprising that urine excretion is diminished, that oxygen consumption is lowered, that the body surface is ischemic and shows evidence of sympathetic nerve dominance.

The foregoing phenomena are inevitable consequences of a critically depleted plasma volume. That such a deficiency exists in most cases of shock is certain. But it has also been shown that shock can exist in the absence of a demonstrable deficiency of plasma volume. There is, therefore, justification for assuming that plasma volume deficiency is not the sole etiology of secondary shock, and that in certain circumstances, to which we shall return later, additional blood or plasma is not the essential need. In the more

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common conditions, where a deficiency may be assumed to exist, the adequate and early replacement of the plasma deficiency will restore the organism, but not if the shock state *has persisted for some time*, even in such a relatively simple situation as shock following hemorrhage. The popular explanation for this failure is that the replaced blood or plasma fails to remain in the blood stream, owing to damage to the capillary walls.

Direct evidence for the existence of capillary damage outside of areas of injury is meager and unconvincing. Capillary damage is seen in the hemorrhagic intestine, in the petechial hemorrhages in the lung and brain or burn shock,¹ and in the adrenal cortex in a variety of conditions culminating in shock. These changes are not seen in all types of shock, nor do they signify the existence of a generalized increase in capillary permeability. Nevertheless, since a large plasma loss may occur through capillaries, which seem intact microscopically, and since such a plasma loss, if uniformly distributed, may exist without producing overtly wet tissues, it becomes necessary to determine the validity of the capillary leakage hypothesis by less equivocal technic than have been utilized heretofore.

This report deals, among other things, with a study of the capillary leakage hypothesis in shock by a technic involving the use of radioactively-tagged plasma proteins*. We shall present evidence (1) invalidating the theory of leakage due to a generalized increase in capillary permeability, and (2) other data which indicate that the peripheral vascular collapse is a state of progressively increasing stagnation of the blood in the capillary bed leading to deterioration of tissue function.

CAPILLARY LEAKAGE IN HEMORRHAGIC, TOURNIQUET AND BURN SHOCK

METHOD By tagging the plasma protein molecule with a radioactive element, and introducing such plasma protein into the blood stream, an unmistakable label is provided by which to identify the movement of plasma proteins. In order to obtain as physiological a preparation as possible, radioactive cystine was synthesized from radioactive sulfur (80-day half-

* The capillary leakage hypothesis assumes that plasma (or some of its constituents) escapes from the general capillary bed at a greater than normal rate and that it fails to return to the circulation as fast as it leaves, resulting in a net gain of plasma to tissues outside of localized areas of injury. Since the net loss of the non-protein fraction of plasma without a simultaneous net loss of some protein from the circulation will not produce shock (except in the case of shock from extreme and rapid dehydration), a determination of the presence or absence of a net gain of plasma protein to the extravascular portion of the tissues outside of areas of injury should decide whether or not this hypothesis is tenable. (See further discussion under section on Burn Shock) In the subsequent discussion, therefore, while the data obtained refers only to protein shifts, we shall not distinguish between plasma protein loss and whole plasma loss when referring to the concept of leakage due to a generalized increase in capillary permeability. For the purpose at hand, it is not so necessary to demonstrate the existence of an increase in capillary permeability as it is to observe the consequences of such an increase.

life) and fed to plasma protein-deficient dogs, which incorporated the cystine into their own plasma proteins. Plasma protein removed from these dogs was then administered to normal dogs and to dogs shocked by hemorrhage, and its rate of escape from the circulation determined. The number of experiments possible was limited by the scarcity of radioactive sulfur and by the very considerable problem involved in obtaining an adequate amount of radiosulf-plasma protein^{2, 3, 4}. As a substitute for the latter, radioactive bromine (34-hour half-life) or iodine (8-day half-life), coupled directly with plasma protein, was utilized. Although radioiodoprotein and radiobromoprotein, so prepared, is denatured, the amount of iodine or bromine incorporated into the protein molecule was minimal and provided a tagged substance whose disappearance rate from the blood in normal dogs was close enough to that of radiosulfprotein to justify its use as a reliable modality for the problem at hand^{5, 6}.

In addition to curves of disappearance from the circulation of radioiodo- and bromoprotein, the tissue content of radioactive protein was determined simultaneously. This is necessary because it is not possible to calculate whole plasma loss from blood disappearance curve unless the plasma volume is known with certainty. Since all methods of measuring plasma volume, which depend on dilution of a dye or tagged substance, measure only circulating plasma, reliable calculations of plasma loss are not possible by such techniques under all circumstances, especially during the shock state. The direct determination of the protein which has actually left the circulation, by analysis of the tissue content of radioactive protein, constitutes a method independent of plasma volume measurements. This method also provides a means of determining whether or not a preferential leakage into certain areas occurs.

The radioactivity due to intravascular radioactive plasma protein was subtracted from the total tissue radioactivity in order to calculate the extravascular plasma protein. The intravascular plasma content of tissues (and its radioactivity) was calculated from the red cell content of each tissue, as determined by hemoglobin measurements (see below) and the estimated^{5, 6, 7} capillary hematocrit. Whenever possible, dogs were exsanguinated at the end of the experiment to reduce the intravascular content of blood in the tissues to a minimum.

In each experiment an unshocked dog served as the control and the dose of radioactive protein injected was generally in proportion to body weight. The amount of protein injected was never sufficient to alter plasma volume significantly. The time from injection to the end of the experiment was the same in both control and shocked dogs. The latter received the radioactive protein before or after shock was induced. Graded hemorrhage, a burn, or a tourniquet⁸ was used to produce shock. Except for five early experiments under intravenous sodium barbital, no anesthesia, except novocain for local incisions, was used, but morphine was given to all dogs.

TRAUMATIC SHOCK

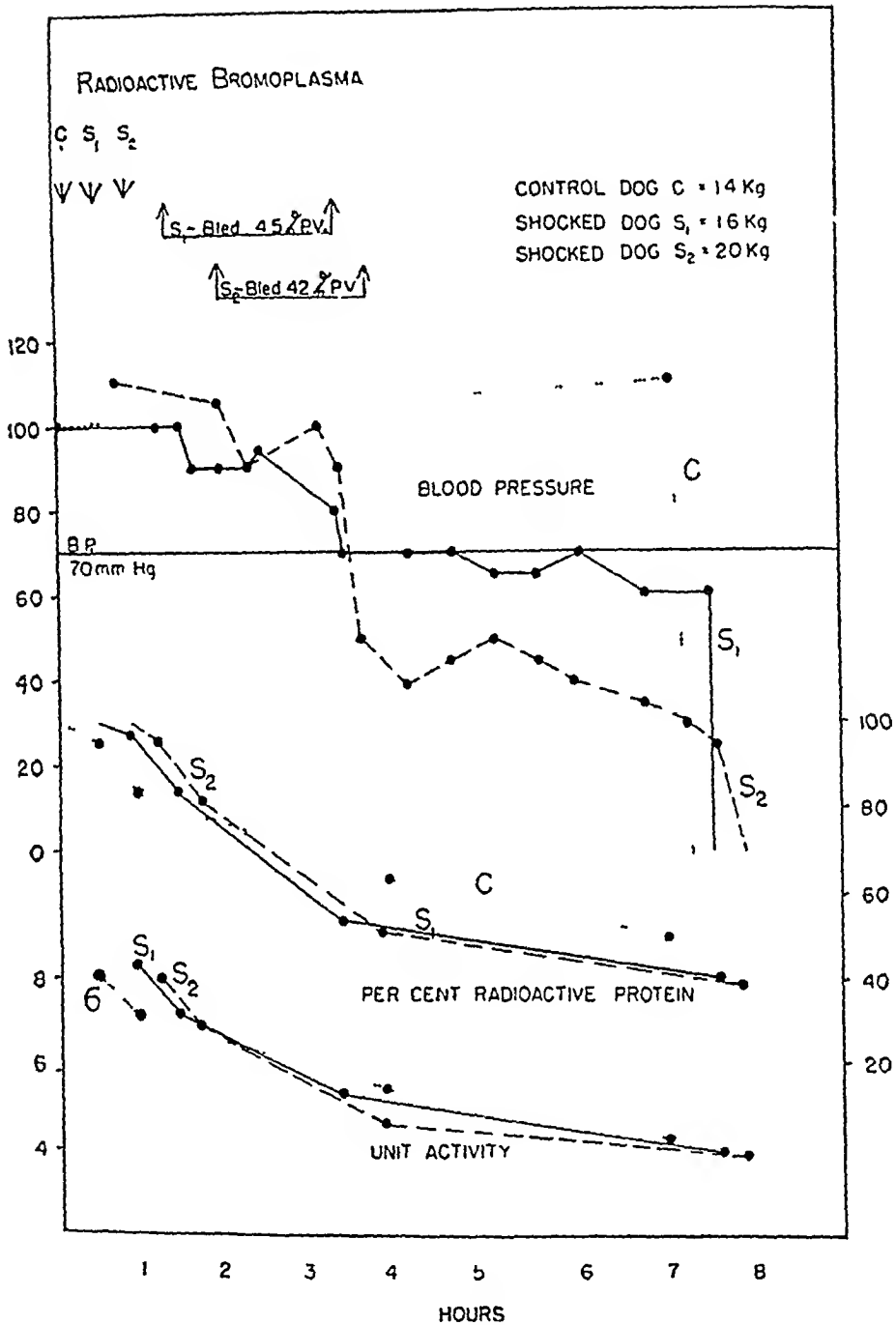


FIG 1—Experiment B—II The increased slope of both radioactivity curves for Dogs S₁ and S₂ as compared to that of Dog C, immediately after bleeding is probably due to dilution by mobilized extravascular fluid. Their subsequent parallel course indicates that the shocked dogs did not lose radioactive protein from the plasma at a greater rate than the control dog. There is no difference in the disappearance curves between the dog in deep shock (S₂, probably irreversible) and the dog in less severe shock (S₁, probably reversible). (Reproduced with the permission of the Journal of Clinical Investigation)

at the beginning of each experiment. The burns were produced under ether by immersion in water at 98° C for varying periods.

No therapy for shock was given, except in the late shock phase of some experiments, when intravenous fluids were injected to see whether an increase in capillary permeability, which may have developed during this phase, could be made manifest by flooding the circulation with a sufficiency of fluids to allow excessive leakage, if this were possible.

Some fourteen experiments were performed, most of which included tissue analyses for lost plasma protein. The full account of the technics and calculations involved in these procedures is published elsewhere^{5, 6}

RESULTS

A HEMORRHAGIC SHOCK

The detailed results of seven experiments with radiobromoprotein will not be analyzed here since they are available in a recent publication⁵. It will be sufficient to reproduce our experience in a typical experiment.

Experiment No B-11 Three morphinized dogs, C (control), S₁ (to be bled into reversible shock), and S₂ (to be bled into irreversible shock), were given radioactive plasma protein intravenously in protein to their body weight. Dogs S₁ and S₂ were then bled into shock. The blood pressure was followed and blood samples were taken at varying intervals until Dog S₂ died. At this time Dogs C and S₁ were exsanguinated and samples of different tissues (Table I) from all three dogs were taken for analysis of

TABLE I
RATIO OF TISSUE RADIOACTIVITY OF SHOCKED DOGS TO CONTROL DOG*

Tissue	<i>Experiment B-11</i>	
	Dog S ₁ Per Cent	Dog S ₂ Per Cent
Liver	59	99
Lung	110	91
Kidney	185	125
Stomach	67	83
Ileum	66	68
Colon	67	56
Skin (thorax)	215	235
Skin (back)	130	110
Heart	130	135
Muscle (foreleg)	110	88
Muscle (spinal)	89	88

* A ratio of 100 per cent indicates equal radioactivity per gram of tissue in control and shocked dogs. Less or more than 100 per cent signifies a lower or higher radioactivity per gram of tissue in the shocked dog.

Ratios varying between 75 and 125 per cent are considered within the limits of experimental error in the experiments with radiobromoprotein. See footnote on page 244.

intravascular and extravascular radiobromoprotein content. The disappearance of radioactive bromoprotein from the blood is charted in Figure 1 in terms of (a) radioactivity per cubic centimeter of circulating plasma, and (b) total circulating radioactivity in per cent of the original amount injected. The latter is calculated as the product of the determined plasma volume and the unit radioactivity. The slope of both curves for Dogs S₁ and S₂ immediately after bleeding shows an increase as compared to Dog C, probably due to dilution by mobilization of extravascular fluid⁹. But the subsequent parallel course of all three curves indicates (1) that the dog in deep shock did not lose radioactive protein from the circulating blood plasma at a

greater rate than the control dog, and (2) that the dog in deep shock did not lose radioactive protein faster than the dog in moderate shock

Analysis of the tissues of the three dogs showed further that the extra-vascular plasma protein content of all tissues, except kidney and skin of thorax, did not differ substantially from one another (Table I). The calculated protein and plasma loss into kidney and skin of thorax was, furthermore, not significant quantitatively.

With certain minor variations similar results were obtained in most of the comparable experiments performed with radiobromoprotein.

The foregoing experiments provided no evidence of greater leakage of protein in irreversible shock than in reversible shock. An increase in capillary permeability to protein that may have developed in the former might have been elicited if the stagnant or collapsed capillaries had been supplied with a sufficient volume of fluid to force fluid transfer. Accordingly, experiments were carried out in which a transfusion was given to two shocked dogs when one had become irreversible. The following is a representative example.

Experiment I-7 The two dogs (Nos. 98 and 99) were bled into shock by hemorrhage. After seven and one-half hours in shock, when the blood pressure was 20 mm Hg, Dog 98 was given a transfusion of 470 cc of plasma containing radioiodoprotein. At the same time a transfusion of 345 cc of plasma containing radioiodoprotein was given to Dog 99, which had been in shock for three hours, when the blood pressure was 30 mm Hg. Dog 98 did not recover and when the blood pressure again declined to 25 mm Hg the blood pressure of Dog 99, which was recovering, was 100 mm Hg. Both dogs were exsanguinated simultaneously, Dog 98 yielding 70 cc and Dog 99 230 cc of blood. Tissue samples for analysis were taken immediately from both, with results shown in Table II, in which the ratio of radioactivity content per gram of tissue of Dog 98 to that of Dog 99 is given.

TABLE II
 RATIO OF RADIOACTIVITY (RADIOIODOPROTEIN) OF TISSUES OF DOG IN IRREVERSIBLE HEMORRHAGIC SHOCK AS COMPARED TO CONTROL DOG IN REVERSIBLE HEMORRHAGIC SHOCK, INCLUDING PLASMA LOSS IN WHOLE ORGANS IN SHOCKED (IRREVERSIBLE) AS COMPARED TO CONTROL (REVERSIBLE SHOCK) DOG*

<i>Experiment I-7</i>		
Tissue	Ratio Per Cent	Plasma Loss Cc
Liver	13	0
Lung	32	0
Kidney	87	0
Intestine	68	0
Spleen	112	1
Skin	41	0
Heart	62	0
Muscle	121	9.5
Total		10.5

* Ratios varying between 95 and 105 per cent are considered within the limits of experimental error in the experiments with radioiodoprotein.

Except for muscle and spleen, all the tissues of Dog 98 contained less extravascular plasma than those of Dog 99. There is, accordingly, no evidence of greater leakage of plasma in the dog in irreversible hemorrhagic shock as compared to the dog in reversible shock. On the contrary, the former, probably because of a less efficient capillary circulation, seems to have displayed a slower than normal rate of escape of iodoprotein from the circulation.

Since the forces operating to produce lethal shock are not necessarily the same in all types of shock, it became necessary to obtain data on the question of generalized increase in capillary permeability in conditions other than hemorrhage. Tourniquet shock and burn shock were studied by the above described technique, using radioiodoplasma protein, which turned out to be the most advantageous preparation of the three types of radioactive plasma utilized in this study. Tourniquet shock and burn shock differ from hemorrhagic shock in that (1) a local loss into areas of injury occurs, and (2) such injured tissues perhaps may liberate a substance capable of affecting capillary permeability in general.

B. TOURNIQUET SHOCK

A tourniquet was applied at the groin to one or both legs of a dog under morphine (3 mg per Kg) and left on for some seven hours. Plasma volume was then measured and radioiodoprotein was given to this dog and to a normal morphinized dog in equivalent amounts. The tourniquet was removed and the same measurements as in Experiment I-7 made. The detailed data is available elsewhere.⁶ Table III lists the tissue analyses of four dogs (I-2 A, I-2 B, I-3 and I-4) showing plasma protein loss in various tissues including the tourniqueted extremities. While the ratio* of the radioactivity content of the shocked dog's tissues to that of the control dog's tissues indicates loss of protein into some tissues other than the ex-

* When radioiodoprotein is used, any ratio below 95 or above 105, except in muscle, is taken to represent a difference outside of experimental error. This error is much smaller than in the case of radiobromoprotein.⁷ The significance of such ratios is not evident in the ratio figures themselves since two factors of importance affect the calculation. These are the relative weights of the organ and the relative radioactivity measurements of such organs per gram. For example, if a ratio of 200, derived from a radioactivity of 0.01 div per sec on the electroscope in the control and a radioactivity of 0.02 div per sec in the shocked dog, applies to a gram of tissue of a given organ (A), and the same ratio, derived from a radio-activity of 0.001 div per sec in the control and 0.002 div per sec in the shocked dog, applies to a gram of tissue of another organ (B) of the same weight, the difference in radioactivity per gram of tissue will be 0.01 for organ A and 0.001 for organ B. The total radioactive protein content of organ A will be ten times that of organ B and the quantitative loss involved is obviously far less in organ B, even though the ratio is the same for both. The relative activities of various tissues in normal dogs are shown in another publication.⁵ The quantitative significance of an increased ratio is of little consequence in an organ like the kidney, which is small in weight, and the same is true when a large organ has a very low order of radioactivity.

tremities, such loss involves only one to three tissues and in no case is the total loss outside of the extremities quantitatively significant, from the point of view of plasma protein depletion. There is, therefore, no evidence that a change in permeability to proteins, outside the area of injury, if it exists, is of consequence in the development and progression of shock following the removal of a tourniquet.

The volumes of plasma lost into the tourniqueted extremities is of course large. The gain in weight was not determinable in Experiments I-2 A and I-2 B, where both legs were injured, but in Experiments I-3 and I-4 the weight increase (above the opposite normal leg) was much greater than the plasma gain determined by radioactivity assay of the tissues (Table IV). This discrepancy is far in excess of errors in method. The difference, therefore, in major part, represents a gain in tissue water drawn from outside areas.

The plasma gain in the leg in three of the four shocked dogs listed in Table III is less than the plasma loss found by circulating plasma volume determinations (Table IV). It was pointed out elsewhere⁵ that in deep shock plasma volume measurements by the dye technic may overestimate loss because the segregation of more plasma into the stagnant peripheral bed as shock deepens (a progressive rise in the amount of trapped plasma) will increase the extent of incomplete mixing and so give too low a dye dilution figure in terms of the total plasma volume. Hence one may expect a discrepancy between the dye method and the tissue radioactivity method, the former showing a falsely higher loss, the more stagnant the peripheral bed becomes. But the much greater total fluid loss into the leg, found by actual weight change, than is disclosed by the dye method again points to a large access of tissue water derived from extravascular sources.

C BURN SHOCK

Three experiments were performed in which one or more extremities were immersed under ether anesthesia for varying intervals in water at 98° C (Tables III and IV). In Experiments I-5 and I-6 radioiodoprotein was injected intravenously into a normal dog and into the burned dog before the burn was produced. In Experiment I-8 the technic was varied in order to see whether the capillaries were more permeable to protein in a severely burned than in a mildly burned animal. For this purpose two dogs were burned, one for 120 seconds, the other for 20 seconds. Four hours before death of the more severely burned dog a plasma infusion containing radioiodoprotein was given simultaneously to both dogs.

The extravascular radioactive protein content of the tissues in all three experiments showed no significant difference in the plasma protein content of the unburned tissues of the burned dog in comparison with the same tissues in the unburned control dog (Exper I-5 and I-6) or the less severely burned control dog (Exper I-8).

TABLE III

RATIO OF RADIOACTIVITY (RADIOIODOPROTEIN) OF TISSUES OF DOGS IN TOURNIQUET OR BURN SHOCK AS COMPARED TO CONTROL DOGS INCLUDING PLASMA LOSS IN WHOLE ORGANS IN SHOCK AS COMPARED TO CONTROL DOGS

Tourniquet Shock										Burn Shock											
Exper No	I-2A			I-2B			I-3			I-4			I-5			I-6			I-8*		
	Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc		Ratio Per Cent	Plasma Loss—Cc	
Liver	97	0		0†	0		118	2 6	64	0	0		0	0		53	0	140	15		
Lung	100	0		0	0		230	7 0	120	2 0	0		0	0		70	0	147	9		
Kidney	176	1 3		0	0		109	0 7	95	0	130		2 1	47	0	0	0	0	0		
Intestine	222	33		15	0		96	0	52	0	155		20	17	0	57	0	0	0		
Spleen	170	2 0		0	0		132	0 4	155	1 4	140		0 7	90	0	0	0	0	0		
Skin	0	3 6		185	3 5		86	0	66	0	23		0	150	5	114	3	0	3		
Heart	75	0		104	0 4		95	0	67	0	100		0	75	0	94	0	0	0		
Muscle	76	0		0	43		138	7 0	104	3 5	57		0	120	7	116	10	0	10		
Injured extremities	400	102		0	132		2800	122	950	180	310		190†	2200	445†	300	24§				
Totals		143			179			140		184			213		457		61				

* The control dog in this experiment was also burned one more severely than the other to compare severe and mild burn shock states

† Where no radioactivity is found in the extravascular tissue of the shocked dog the ratio becomes zero

‡ If loss of plasma is assumed to have occurred early after the burn these values would be halved

§ Plasma loss into the burned legs was calculated by comparison with values for intact muscle and skin for both dogs Plasma loss in milder burn was 38 cc Small loss was due to the fact that leakage occurred before radioiodoprotein was given (four and one half hours before the end of the experiment)

TABLE IV

PROTOCOL DATA IN TOURNIQUET SHOCK AND BURN SHOCK AND COMPARISON OF PLASMA LOSS INTO INJURED EXTREMITY BY THREE CRITERIA

Type of Shock	Exper No	Dog No	Dog Wt	Ws Ic*	Ic Ic	Duration of Tourniquet (hours)	Duration of Exper after Removal of Tourniquet or Burn	Blood Pressure at End of Exper	Volume of Exsanguination at End of Exper	Hematocrit Increase	Decrease in P V by Dye Method†	Wt Increase of Injured Extremity	Plasma Loss into Injured Extremity by Radioactivity Analysis of Tissue‡	Remarks
			Kg			Hours		Mm Hg	Cc	Per Cent	Cc	Gm	Cc	
Tourniquet	I-2A	84	8 7	1 0		5	5 7	75	270	8	300		102	Tourniquet on both hind legs
		85	6 9			control		110	160	0				
	I-2B	86	10 6	0 93		8	4 0	0	0	13	307		132	Tourniquet on both hind legs
		87	5 1			control		110	200	0				
	I-3	88	11 8	0 92		10 5	5 7	10	30	16	257	360	122	
		89	14 1			control		120	500	0				
	I-4	90	13 4	1 0		7 5	11 5	30	100	4	220	435	180	After 7 hours the increase in hematocrit was 13% (Dog 90)
		92	8 2			control		105	150	0				
	I-5	94	8 5	0 98		45	27	0	0	1	45	121	190	Burn of foreleg and hind leg B P remained at 80 Mm Hg and dropped to 30 Mm Hg after a small dose of nembutal (Dog 94)
		95	5 0			control		110	200	0				
Burn	I-6	96	11 6	1 0		90	18 5	0	0	16	230		445	Burn of both hindlegs
		97	10 6			control		110	480	2				
	I-8	200	11 8	1 0		120	22	30	0	8	785	69	24§	Plasma infusion (325 cc) with radioprotein
		201	10 1			20	21	95	150	11	250	171	38§	Plasma infusion (270 cc) with radioprotein

* Formula showing relative proportion of radioiodoprotein dosage to weight of shocked versus control dog, when W = wt of dog, I = volume of radioactive plasma injected c = control dog and s = shocked dog

† In burn experiments plasma volumes by dye method were complicated by marked hemolysis

‡ Data from Table III

§ Since tagged infusion was given four and one half hours before end of experiment loss during this period only was determined

In Experiment I-5 and I-6 there is no correspondence between the plasma volume loss into the burned extremity, as estimated from radioactive plasma protein content, and the loss as measured by intravenous dye. The unavoidable hemolysis of blood in burned dogs affects the reliability of the latter method.

In Experiment I-8 the radioactive protein content was injected too late to permit a determination of total protein loss into the burned area. In the severely burned dog the very small increase in weight of the burned extremity suggests that peripheral vascular collapse was due to factors other than plasma volume deficiency.

Although the extent of the plasma volume loss into the tissues in the foregoing experiments cannot be assessed with complete accuracy, the loss outside of areas of injury involves only one or two tissues, which vary from one experiment to another, and, in any case, is not quantitatively significant.

The calculation of plasma volume loss into tissue is based on the assumption that if such loss occurs outside of areas of local injury, whole plasma is lost. If greater capillary permeability to the nonprotein than to the protein fraction of the plasma should exist, the disproportion between the loss of the protein and the nonprotein fraction of plasma would be reflected in a shift of the total protein concentration. Since the latter does not increase in hemorrhagic shock,¹⁰ plasma if lost would be in proportion to protein loss in hemorrhagic shock, except perhaps when saline infusions are given in the late shock phase. The rise in total protein concentration in burn shock and in tourniquet shock may be explained as due to a disproportionate loss of the nonprotein fraction into or outside the injured area. Such loss, if substantial, into tissues outside the injured area would not be likely without a loss of a measurable amount of protein. Since no protein is lost (*i.e.*, no loss of consequence, except in a sporadic and inconsistent manner involving one or two tissues varying from one experiment to another) into areas outside the locally traumatized area in either burn shock or tourniquet shock, our assumption that no plasma is lost outside of areas of local injury seems justified.

Evidence that plasma does not escape from the general capillary bed in untreated shocked dogs appears in plasma volume measurements in 24 dogs in hemorrhagic shock listed in Table V. These showed an average gain of nine per cent above the expected amount, owing to mobilization of extravascular fluid during an early phase of shock. In 12 of these experiments plasma volume was measured again after a subsequent interval of shock. In seven of these no therapy was given and the volume was substantially unchanged. The remaining five received a saline, plasma or blood transfusion in the late shock phase, with an average volume 19 per cent below what was expected from the volume of the infusion added to the previous volume determination. The discrepancy between the expected and determined volume might have been due to loss into tissues (particularly in the case of saline infusion), but it might also have been due to inadequate

TABLE V*
PLASMA VOLUME IN HEMORRHAGIC SHOCK
Plasma Volume in Shock

Expt No	Plasma With- drawn to Produce Shock Per Cent	First Measurement				Second Measurement				Remarks
		Dura- tion of Shock Hours	Ex- pected Per Cent	Found Per Cent	Gain or Loss Per Cent	Dura- tion of Shock Hours	Ex- pected Per Cent	Found Per Cent	Gain or Loss Per Cent	
1	46	1½	54	76	+22	4½	73	69	-4	
2	46	1	54	67	+13					
3	63	1	37	55	+18					
4	60	1½	40	60	+20	4½	55	57	+2	
5	71	3	29	54	+24					Bleeding continued during shock
6	35	2	65	46	-19					
7	36	3	64	64	0					
8	45	1½	55	63	+8	3	56	56	0	
9	44	2½	56	72	+16					
10	28	3½	72	66	-6	4½	63	66	+3	
11	45	1	55	65	+10					
12	39	10	61	65	+4					
13	34	6	66	64	-2					
14	61	5½	39	75	+36					
15	40	2½	60	81	+21	4	61	65	+4	
16	25	1½	75	96	+21	3	85	85	0	
17	20	1	80	84	+4					
18	42	3	58	78	+20	4¼	71	75	+4	
19	58	4	42	51	+9					
20	36	2½	64	53	-11	5	85	78	-6	2nd reading 1½ hrs after blood trans fusion
21	42	2½	58	64	+6	7	106	90	-16	2nd reading 3 hrs after blood trans fusion Recovered
22	15	1	85	70	-15	2	123	98	-25	2nd reading ¼ hr after plasma trans fusion
23	42	3½	58	58	0	4	97	87	-10	2nd reading ½ hr after plasma trans fusion
24	68	2	32	59	+27	2½	119	85	-34	2nd reading ½ hr after 500 cc saline infusion

Average
All dogs died except as noted

+9.3

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mixing of dye with capillary blood since the validity of the dye method for total plasma volume measurement depends on complete mixing of the dye with the peripheral blood. If in the late shock phase the peripheral blood is not in active circulation, in the same sense as the peripheral waters of a swamp, through whose center a brook runs, are not in active circulation, complete mixing may not occur in the time interval allowed (15-30 minutes). The results with respect to plasma loss obtained by the dye volume method may be said not to disagree with those obtained by the radioactive protein technic.

STAGNATION (OR TRAPPING) OF BLOOD IN THE PERIPHERAL CIRCULATORY BED

That stagnation can explain the discrepancy between expected and observed plasma volumes in the late phase of shock may be inferred from a variety of data: (a) The steadily declining venous oxygen concentration, (b) the increasing divergence in plasma p_{H} values in favor of a relatively greater acidity on the venous side of the circulation, (c) the increasing divergence in the plasma CO_2 values due to the lesser fall in CO_2 concentration on the venous side of the circulation, (d) the obviously slow or even absent flow through much of the peripheral bed in deep shock, as seen by

capillary microscopy in the rat's mesentery¹¹ and dog's omentum, and (e) the reversal of all these changes in the direction of normal during the transient recovery phase following a large saline infusion¹²

In collaboration with Gibson and Evans,⁷ who will publish the full data elsewhere we have obtained evidence that the peripheral circulatory bed and its contained blood is, so to speak, out of contact with the central circulation, and that much of the blood in the latter traverses a shortened circuit. It may be sufficient here to refer briefly to the technic utilized and to quote a few representative results

Morphinized dogs were given an intravenous dose of red cells containing radioactive iron (47-day half-life) and the red cell volume was determined by the same technic as is used for plasma volume by the dye method. The plasma volume was also measured at the same time. Bleeding into shock was then performed, and after some hours in shock an additional dose of radioactive red cells was given. In a number of experiments the resulting increase in radioactivity per cubic centimeter of cells was more than the expected amount. The red cell volume calculated on the basis of these data was less than the expected volume allowing for the volume of red cells removed by bleeding. This is regarded as evidence of stagnation of red cells somewhere in the peripheral bed.

Further evidence of stagnation (or trapping) was obtained as follows. Dogs in hemorrhagic shock received a dose of radioactive red cells. Upon death of the dog the number of red cells in cubic centimeter per gram of tissue was determined by two methods

$$\begin{aligned}
 & \text{A } \frac{\text{Hb in 1 gram tissue}}{\text{Hb in 1 cc arterial blood (just before death)}} \times \text{arterial hematocrit} \\
 & \text{B } \frac{\text{Radioactivity (Fe*) per gram of tissue}}{\text{Radioactivity (Fe*) 1 cc arterial blood (just before death)}} \times \text{arterial hematocrit}
 \end{aligned}$$

Formula A is a method of direct determination of the total number of red cells in cubic centimeter per gram of tissue, but formula B is a determination of the true number of red cells in cubic centimeter per gram of tissue in sufficiently active circulation to have reached the tissue from the time of injection until death. The discrepancy between the results of the two formulae is a measure of the incompleteness of the mixing and therefore of the extent of trapping of blood out of active circulation. The average ratio of B/A was found to be 1.0 ± 0.1 in nine normal morphinized dogs. The average ratio in the shocked dogs was 0.7 to 0.8, indicating that some 20 to 30 per cent of the red cell volume in tissues was trapped in the peripheral bed, i.e., by-passed by the active stream.

Such a degree of trapping could not be demonstrated with equal uniformity for plasma. Possibly this may be due to a partial balancing of trapped plasma by mobilized extravascular fluid. It may also be that in

shock the mixing of plasma in active circulation with that in the peripheral bed is physically easier than is the case for particulate material such as red cells. The latter hypothesis is thought not to be true for the normal dog according to Hahn, *et al*¹³

As shock deepens the trapping may be expected to increase. In recent experiments the technic adopted for measuring the volume of trapped blood was altered in order to avoid errors (see below) inherent in hemoglobin measurements for determination of blood content. This was done as follows: A dose of radioactive red cells, containing radioactive iron with a five-year half-life, was injected during the preshock phase and when the dog was in late shock, a dose of radioactive red cells with a 47-day half-life was injected. The latter, insofar as it might fail to mix completely, would show a deficiency in the previously determined total red cell volume due to trapping.

Analyses of the tissues for the two types of radioactive iron was then made. The number of red cells in cubic centimeter per gram of tissue was then calculated on the basis of the content of each type of radioactive iron.* The two determinations would be expected to agree if complete mixing occurred when both types of radioactive red cells were injected. If stagnation were present when the second dose (47-day half-life radioactive iron) was injected, the cubic centimeter of red cells per gram of tissue, calculated on the basis of 47-day half-life radioactive iron, would be less in proportion to the degree of stagnation. This was found to be the case.

On an average, the tissue content of 47-day half-life iron was some four-fifths of that of five-year half-life iron. Dilution of the second dose of radioactive red cells was likewise approximately four-fifths of the expected amount. The ratios by both technics indicate that there was stagnation of some 20 per cent of the red cell volume of tissues.

An even more extensive segregation of blood in the peripheral bed was observed in Experiment 1-8 (Table IV), in which a severe burn was inflicted on one hindleg of a dog weighing 11.8 Kg. Twenty-two hours later the dog was in deep shock, but the hindleg gained only 69 grams in weight. The original plasma volume was about 600 cc and 325 cc of plasma had been infused. By the dye plasma volume method a subsequent decrease or "loss" of 785 cc in plasma volume was measured. This value may be too high due to marked hemolysis from the burn. However, since little loss occurred into the leg as indicated by the small weight gain and a rise of only eight per cent in hematocrit, the loss indicated by the dye volume method was obviously loss out of active circulation, but not loss from the capillary bed.

In burn shock and in other types of trauma plasma is continuously lost because of the leakage *at the site of injury*, but leakage through the general

* Prof. Robley Evans, and coworkers, of the Massachusetts Institute of Technology constructed Geiger counters which are capable of distinguishing between and accurately determining the radioactivity of the two types of iron in the same blood or tissue sample.

capillary bed does not occur. In hemorrhagic shock an initial loss of plasma is produced, but a progressive decline in plasma volume cannot be demonstrated because leakage does not occur through any capillary area. The difference between the hemodynamic disequilibrium in such states of shock in which there is continuing local loss and that of shock due to hemorrhage, in which hemorrhage has stopped, is merely a quantitative rather than a qualitative one. Once a sufficient initial decline in plasma volume occurs in any type a fatal mechanism is in operation and it is, therefore, not necessary to explain death from shock as involving a *progressive* loss in plasma volume.

On the other hand, the foregoing data (on stagnation or trapping) demonstrates that shock is a state in which a progressive decline in *effective circulating plasma volume* exists. *The total plasma volume may be deficient, but this is not always so.* Thus, if shock is precipitated by an initial critical loss of plasma, a deficiency will be present, if shock is precipitated for some other reason, *e g*, severe infection or toxemia, a deficiency in plasma may not be present. Ebert and Stead¹⁴ could find no deficiency in the plasma volume of eight patients in shock as a result of severe coccal infection. It is possible that here, as in the case of our hemorrhagic shock experiments (Table V), a deficiency might have been observed in a later phase of shock. But again, such a deficiency could well be explained as due to incomplete mixing with blood which is stagnant in peripheral areas.

Since shock can exist in the absence of a demonstrable fall in plasma volume, or after replacement of a known deficiency, and since the replaced plasma does not leave the circulatory bed, the essential *defects in irreversible shock* are (1) *inefficient circulatory distribution of the total blood volume*, and (2) *inadequate velocity of flow through capillaries, even when the blood volume equals or exceeds that present before shock occurred.*

The vascular tree in shock shows widespread vasoconstriction (though it is not maximal). In hemorrhagic, burn or tourniquet shock the small arteries and veins of the omentum in the dog or of the web of the foot or the mesentery in the rat are narrowed and the capillaries are empty or nearly empty of red cells. Chambers, Zweifach and Lowenstein¹¹ have observed dilatation of arterioles, capillaries and venules in a rapidly fatal type of tourniquet shock, in which the extent of the fluid loss into the tourniqueted extremity is limited by a quick collapse resulting possibly from a toxic factor. Terminal relaxation of the arteries (but not of the veins) in the mesentery of the cat in tourniquet shock under barbiturate anesthesia was noted by Page and Abell¹⁵. Whether the dilatation observed by Chambers, *et al*¹¹ and the terminal relaxation observed by Page and Abell occurs in the absence of barbiturate remains to be determined.

These observations, suggesting decreased blood content of the peripheral circulatory bed, receive support from direct estimations of the blood content of the tissues in shock. These were made by the following method.

Weighed amounts (two grams) of various tissues of dogs in shock were taken immediately after death from shock, or in normal dogs, following

exsanguination or intravenous nembutal or potassium cyanide. Blood in large vessels or on the surface of tissue samples was gently wiped away so that only blood in the smallest vessels was left in the tissue. Representative pieces of such tissues as lung, liver, bowel, skin and muscle were pooled and aliquots taken for analysis. The tissues were finely minced, extracted with distilled water at 4° C¹ for 24 to 36 hours, and filtered through gauze. The hemoglobin in the filtrate was measured after clearing with ammonia in a photo-electric colorimeter against standards from arterial blood (taken at time of death), using a 620- and 540-filter to correct for turbidity. No correction for methemoglobin was made. Although inaccuracies in the hemoglobin measurement are unavoidable, the red cell volume in cubic centimeter per gram of tissue agreed by this method sufficiently in experiments with simultaneous red cell content determinations made by the radioactive red cell technique,† to permit acceptance of our results as a fair

TABLE VI

AVERAGE VOLUME RED CELLS (CC) PER GRAM OF TISSUE OF VARIOUS ORGANS IN NORMAL AND SHOCKED DOGS
HEMOGLOBIN AND RADIOACTIVE IRON DETERMINATIONS

Tissue	Normal*	Normal Ex-sanguinated	Hemorrhagic Shock	Tourniquet Shock†	Burn Shock	Normal‡	Hemorrhagic Shock‡
	Cc	Cc	Cc	Cc	Cc	Cc	Cc
Liver	050	011	054	037	043	058	021
Lung	073	038	095	038	071	079	052
Kidney	055	019	035	036	054	047	024
Intestine	0092	0016	017	006	005	011	0033
Spleen	186	021	050	060	120	30	067
Skin	0022	00090	003	002	001	0065	
Heart	0094	0045	017	005	004	018	0082
Muscle	012	0050	021	005	005	0062	000
Injured extremity				005	019		
No. of dogs	7	7	8	5	4	5	1

* Killed by intravenous injection of nembutal or cyanide (two dogs)

† Some of the dogs received infusions of blood (2) plasma (3) or saline (1) and (3) were exsanguinated

‡ Determination by radioactive red cell measurement

approximation to the facts (Table VI). From the hemoglobin value the red cell content per gram of tissue was calculated from formula A given above. The liver, lung, kidney and spleen are the only organs containing appreciable amounts of red cells per gram. When the number of red cells per gram of tissue in dogs in shock is compared to that of the normal dog, there is seldom more, and usually less, in the shocked dog (Table VI).‡ In general, it appears that the red cell volume is not greater and is probably somewhat less than normal in the peripheral circulatory bed.

However, direct estimations of the blood content of the tissues in shock by hemoglobin measurements do not indicate what fraction of the blood found in the vessels of these tissues was in circulation in shock. Such data can be obtained by radioactive iron measurements in tissues after injection of red cells, tagged with five-year half-life iron before shock and of red cells, tagged with 47-day half-life iron during shock as described above.

* Myoglobin of heart and skeletal muscle was first extracted with saline solution following which the residue after centrifugation was extracted with distilled water.

† In collaboration with Gibson, Evans, *et al*.⁷

‡ The acutely exsanguinated normal dog shows fewer red cells per gram of tissue than the nonexanguinated normal dog or the dog shocked by hemorrhage.

The capillary bed normally contains some 20 per cent of the total blood volume. In shock this percentage is not only not increased, but probably is decreased. Data obtained with radioactive red cells indicates that some 20 per cent of this capillary blood volume is trapped out of the active circulation. Although this amount of trapped blood is only some four per cent of the total blood volume, it is, nevertheless, a serious threat to normal tissue function since the capillary bed is the "business end" of the circulation. It is perhaps of no great consequence whether the blood content of tissues at any moment is the same, somewhat more, or somewhat less than normal. The important fact is that this blood, whatever its amount, is not moving at a sufficient velocity through a sufficient number of capillaries to maintain normal tissue function.

COMMENT The extent of the disturbances in tissue function is indirectly indicated by the level of the venous oxygen concentration and the cardiac output. In extreme states of shock the venous oxygen levels are below five volumes per cent, and the cardiac output may be well below 50 per cent of normal. Anuria or oliguria may be due to decreased velocity of flow or to kidney cell injury. Long and Engels¹⁶ report in rats an increase in the blood amino-acid levels due to failure of deamination by the liver as a result of anoxemia of the portal blood vein, the main source of the oxygen supply to the liver. Disturbances in enzymatic function are indicated by the increase in pyruvic and lactic acid blood levels. Alexander,¹⁷ and Lamson¹⁸ find that the thiamin-coccarboxylase mechanism is seriously affected.

The therapeutic problem in shock which has not yielded to adequate plasma volume replacement becomes one of restoring normal velocity of flow through the capillary bed. Capillary and venous anoxemia rise toward normal when the velocity is accelerated.¹² Whether this increase in velocity of flow necessarily involves a simultaneous increase in cardiac output requires further investigation. Pressor amines do not improve velocity of flow or cardiac output in shock.¹⁹ Pure oxygen even at three atmospheres does not significantly improve the peripheral circulation.¹² Other substances which may improve the peripheral circulation in shock are being investigated.

CONCLUSIONS ¹

1 Plasma proteins tagged with radioactive isotopes (S^{35} , Br^{82} , I^{131}) were used to study the capillary leakage hypothesis in hemorrhagic, tourniquet and burn shock. No evidence of leakage due to a change in the permeability of the general capillary bed was found. Tagged plasma proteins escaped into areas of injury in considerable amounts, but not into untraumatized areas.

2 There is no evidence to show that the general capillary bed becomes more permeable to plasma proteins or plasma in the late or irreversible phase of shock.

3 Data obtained by the use of radioactively-tagged red cells injected intravenously combined with tissue analyses for hemoglobin and tagged red

cell content indicate that about one-fifth of the capillary blood becomes stagnant or trapped out of active circulation as the shock phase deepens

4 The progressive decline in shock is not due to a progressive fall in plasma volume but to a progressive fall in the volume of actively circulating plasma

5 The blood content in cubic centimeters per gram of tissue is not more and is generally the same, or less, in shock than it is in normal dogs

6 The therapeutic problem in shock after adequate replacement of lost blood or plasma has failed is one of restoring volume and velocity flow through capillaries before the integrity of vital tissue processes is inevitably lost

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ROLE OF THE NERVOUS SYSTEM IN SHOCK*

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IT HAS BEEN GRADUALLY ESTABLISHED in comparatively recent years that the outstanding cause of surgical shock is the local loss of blood and/or plasma. The accompanying improvements in hemostasis and in the use of blood and plasma transfusions for the prevention and treatment of shock have resulted in marked improvement in surgical results, and in great extension of the field of operative surgery. Operations of great magnitude are now being successfully performed that were impossible before and cases of severe injuries and burns are being saved that previously were invariably fatal. These advances warrant further investigation of other causes of shock in the endeavor to obtain additional improvements in its prevention and treatment.

One of the oldest and most widely entertained theories is that shock may somehow be brought about by an insult to the nervous system. The influence of the nervous system on vasomotor tone may be briefly summarized as follows. Control is exercised through the vasomotor center in the medulla. Efferent impulses pass out from the vasomotor center by way of the spinal cord and sympathetic nerves to the blood vessels. They are both vasoconstrictor and vasodilator, but predominantly the former. Afferent impulses come to the vasomotor center over pathways from the somatic and the modulator or depressor nerves supplying the aortic arch and carotid sinuses and from the cerebral cortex. Both pressor and depressor impulses come from the somatic nerves and were shown, by Ranson and Billingsley,¹ to have separate pathways in the spinal cord. Both vasopressor and vasodepressor centers have been demonstrated in the cerebral cortex of monkeys and cats by Hoff and Green.² Impulses coming over the cardio-aortic or aortic depressor and carotid sinus modulator nerves are entirely vasodepressor.

The most popular conception of neurogenic shock is that it results from marked and prolonged lowering of blood pressure by afferent vasodepressor impulses coming to the medulla either from the injured field over somatic nerves or from the cerebral cortex, where they are set up as in syncope by adverse special sense or pain sense impulses or purely by mental action. Lowering of blood pressure is accomplished by inhibition of vasoconstrictor impulses and possibly, to some extent, by acceleration of vasodilator impulses. Cardiac inhibition is also a causative factor in syncope.

The great objection to this neurogenic theory of shock is the lack of evidence based on carefully controlled clinical studies and on concert experimental methods of production in which other factors, as local loss of circulating fluid, and anesthesia are excluded. It is well known, from animal

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experimentation,^{3, 4, 5} that simple exposure and stimulation of somatic nerves of the limbs, as the sciatic and saphenous, by pinching, crushing, cutting or the application of an electric current of different strengths and frequencies, cause a variety of minor reactions but most frequently an initial reflex fall of blood pressure lasting for one to three minutes, after which the pressure may rise above or return to the previous level. The same has been found true for man, as in case of repeated crushing and pinching of the sciatic nerve during thigh amputation. Following alternating arrest and stimulation with a tetanizing current for one or two hours, the pressure may fall to some extent, but nothing like a state of shock is produced. The same fibers, large and small, are stimulated in the nerve trunks by these experiments as are stimulated in wounds of the extremities, and often much more forcefully. Seven rabbits have been tested during this study, and it was impossible to produce shock by these procedures. Upper abdominal operations⁶ in man occasionally cause rapidly developing bradycardia and a fall of blood pressure to 80, 60 or 50 mm Hg, but the patient remains in good condition, the pressure rises as the intra-abdominal manipulations diminish and the circulation returns to normal unless it has become embarrassed by other factors. The reaction has been explained by the assumption of vasodepressor fibers in the abdominal trunks of the vagi which are stimulated. Further study is indicated in order to determine more accurately the method of production. The marked lowering of blood pressure in fainting^{6, 7} produced by the action of afferent impulses from the brain on heart and vasomotor center is also short-lived as loss of consciousness interrupts the adverse psychic impulses and produced recumbency with brain and heart coming to approximately the same level. Improvements of cerebral blood supply and elevation of blood pressure ensue and consciousness is regained within a relatively short time without harmful after-effects.

O'Shaughnessy and Slome,⁸ and Kabat, Lorber and Welte,⁹ have reported an increased tendency to shock production in case of limb trauma of dogs in which the limb was severed from the body except for the nerves and femur, and the circulation maintained either by perfusion with blood rendered noncoagulable or by crossed-circulation from another animal. However, Blalock and Cressman¹⁰ did not confirm these results except to report that spinal anesthesia reduced the tendency to shock when general anesthesia was then induced by nembutal in cats and chloralose in dogs.

The cardio-aortic or aortic depressor nerves and the carotid sinus nerves are afferent nerves supplying the walls of blood vessels, stimulation of the endings of which by increase of the intravascular pressure causes a reflex fall in blood pressure, chiefly by inhibition of vasoconstrictor impulses from the vasomotor center in the medulla. In this way they serve to modulate blood pressure when it is by any mechanism elevated. Animal experiments have been carried out in which these nerves were stimulated in an effort to determine the effects of a purely neurogenic lowering of blood pressure except as modified by the anesthesia, blood loss from clot washings and

samples for analyses, and by the relatively slight trauma incident to the experiments. The results should be an index of vasodepressor action regardless of the source of the impulses.

Schachter, and the author,¹¹ have reported the results of stimulation of the carotid sinus nerves. In a minority of the experiments, the blood pressure could be maintained in the vicinity of or moderately below 70 mm Hg for hours, by continuous electrical stimulation using a bipolar cannula electrode inserted in the carotid sinus. Initial low shock levels were not obtained. Release of the stimulus at any time up to four or five hours was followed by a prompt rise of pressure to previous levels, but beyond that time both the response to release and the pressure during stimulation usually declined gradually, and death occurred in seven and one-half to nine hours with the animal in a state of shock. When blood pressure fell on stimulation but was maintained above 75 or 80 mm Hg, there was remarkably little impairment of circulation, and the animals lived an average of ten hours longer than those with pressures maintained at 70 mm Hg, or below, and only about ten hours less time than the control experiments.

Cardio-aortic Nerve Stimulation—The cardio-aortic or aortic depressor nerves supplying the arch of the aorta and first portions of its large branches and some fibers to the heart, are more powerful depressor nerves than the carotid sinus nerves and offered a more favorable method of experimental neurogenic lowering of blood pressure. They are fused with the vagi in all animals except rabbits and a certain percentage of cats, for which reason rabbits were chosen for the experiments. Urethane 0.5 Gm per Kg body weight, was given intraperitoneally, which maintained light anesthesia. The femoral arteries were cannulated, one for kymographic recordings of blood pressure, and the other for drawing blood samples and for injections. The mandible was tied to the bit of the head piece of a dog-board on which the rabbit was fastened, the cardio-aortic nerves were isolated alongside the vagi in the neck and a shield electrode attached to a Harvard inductorium receiving six volts from a transformer was applied to each nerve. Blood pressure ranged from 90 to 120 with an average of 105 mm Hg. Control animals with only the stimulus deleted lived 14 to 18 1/2 hours.

In favorable cases stimulation of both nerves, with the secondary coil at nine or ten centimeters from the primary, usually caused a sharp drop in blood pressure to a range of 25 to 60 mm in two or three minutes and slowing of the pulse during the same period from an average rate of over 200 to a range of 60 to 100 per minute. A somewhat stronger stimulus was required to produce a similar effect if one nerve only was stimulated. With continued stimulation, the course of the blood pressure varied greatly according to the individual experiment. In some cases the pressure remained low for hours while in others it rose either rapidly or slowly. In such cases, increase of the strength of the stimulus usually caused a further decline. However, when a very marked decline was obtained by a weak stimulus, as with the secondary coil at nine or ten centimeters, increasing the strength of the stimuli to the

NERVOUS SYSTEM IN SHOCK

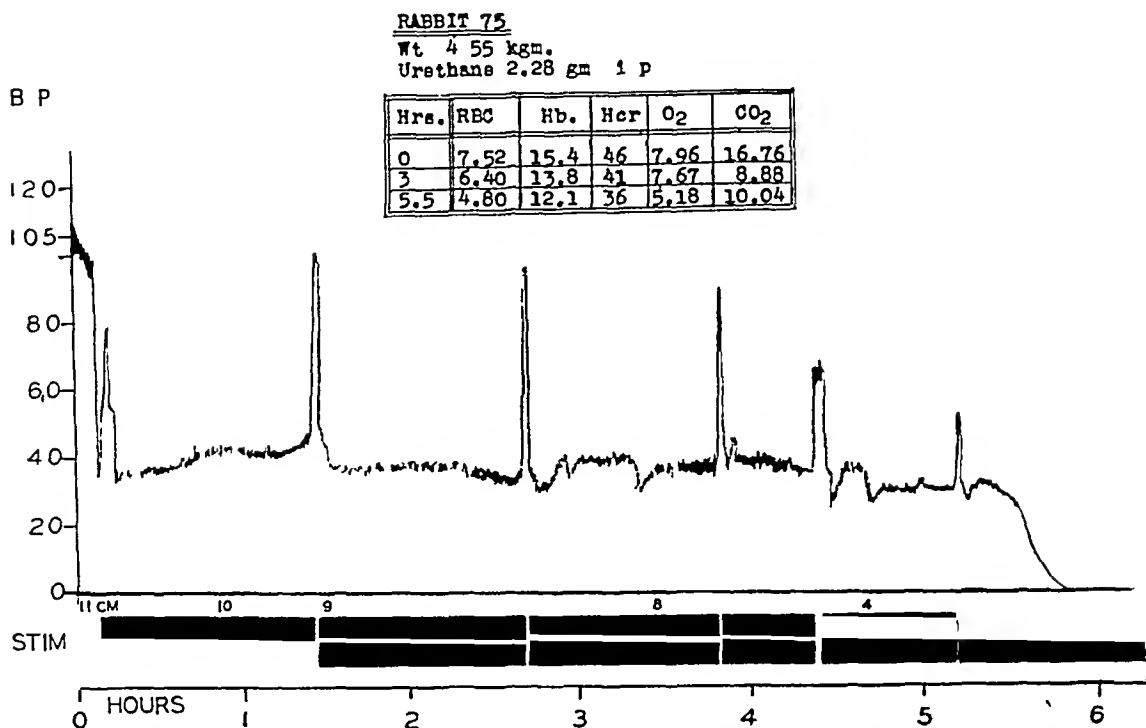


FIG 1—Death from low pressure after a 5.5 hour period of stimulation. Vasomotor center functioned well for four hours, and then gradually failed. Progressive hemodilution and reduction of arterial blood oxygen and carbon dioxide.

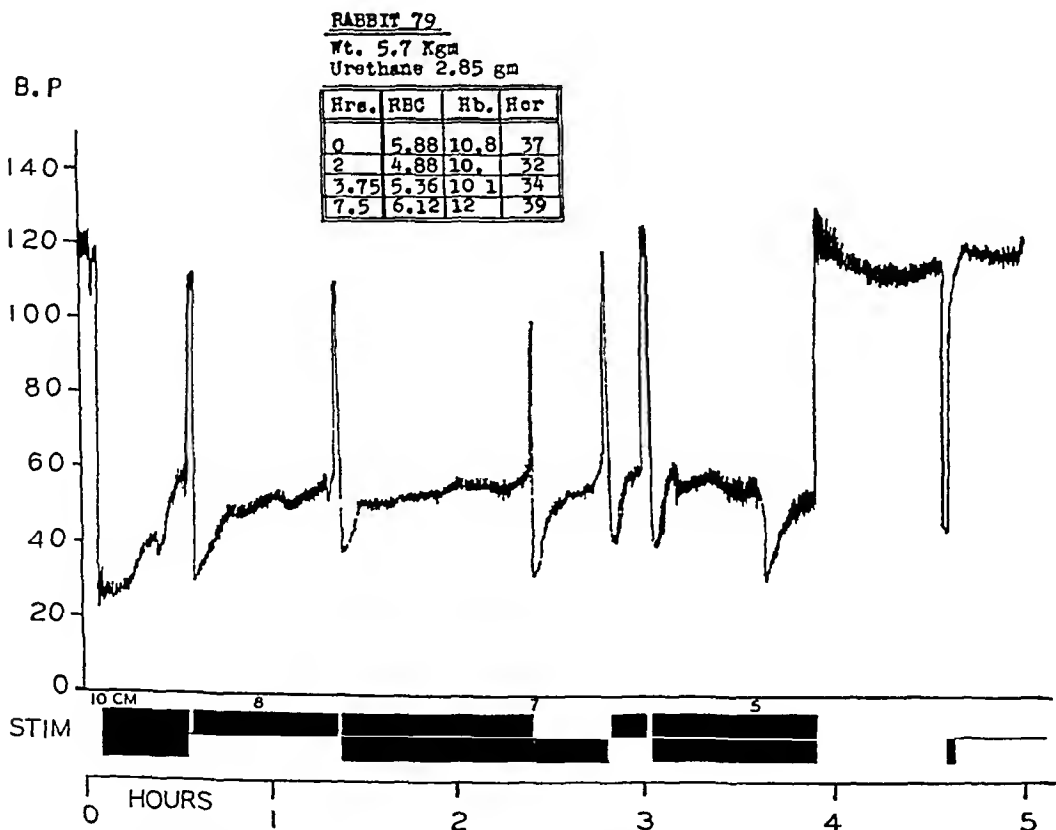


FIG 2—Under depressor nerve stimulation, blood pressure averaged 50 mm Hg for four hours. Vasomotor center never impaired and rapid recovery on stopping stimulus. Killed after 11 hours, with pressure at 90 mm Hg.

maximum of the inductanisms failed to kill the animal, and might fail to cause further lowering of the pressure. The pulse always increased in rate after the initial few minutes, but usually continued somewhat reduced in rate as long as the blood pressure remained low from stimulation. Respirations were little influenced by the stimulus. Traumatism of the very small nerves during preparation, accumulation of blood in the wound and contact with tissues causing current leakage and dying of nerves, are variously responsible for the fluctuations in response.

Extensive experiments have been performed in which blood studies have been correlated with pressure studies and necropsy findings. They are being reported in detail by Laestari, Schafer, Eichelberger, Schachter, and the author, and only an abbreviated account is included here.

When the blood pressure was maintained at low levels by continuous cardio-aortic nerve stimulation, death took place in from 25 to eight hours and, in general, the lower the pressure the shorter the period of survival. In the majority of experiments, the pressure ranged between 35 and 55 mm Hg, and the animals usually lived five to eight hours. Temporary release of the stimulus at intervals during the early and middle portions of the experiment usually resulted in a rapid rise of pressure to the vicinity of the previous level indicating a good state of vasomotor tone. But during the terminal portion (0.5 to 1.5 hours) of the period of survival, the response on release markedly weakened, indicating failure of the vasomotor tone and the blood pressure under stimulation usually declined slightly before death. Blood examination showed hemodilution and reduction of arterial blood oxygen and carbon dioxide. In some cases there was a tendency toward hemoconcentration toward the end. Figure 1 shows an experiment in which, for the first four hours, the blood pressure remained in the vicinity of 40 mm Hg during stimulation and rose to near the original level during the three short intervals when the stimulus was released. From then on, the pressure declined slightly during stimulation and the responses during the two releases had weakened rapidly before death at 5.5 hours. That is, the vasomotor tone was remarkably well preserved for four hours after which it gradually failed. Hemodilution progressed gradually throughout the experiment, except at times in the terminal stages.

When the vasomotor tone was well preserved, permanent release of the stimulus after such periods of depression lasting sometimes for four to seven hours would be followed by rapid restoration of blood pressure to the vicinity of the prestimulation level, and the animals lived on, similar to controls. The blood, which usually diluted during the period of low blood pressure, would show a tendency to concentrate after the pressure was again elevated. These findings are illustrated by Figure 2, in which experiment the blood pressure was maintained at a fluctuating level, averaging about 50 mm Hg for four hours, during which time there was marked elevation with each release. After discontinuation of the stimulation, the blood pressure rose to the previous level, and seven hours later, when the animal was killed, it still registered

90 mm Hg The blood which had slightly diluted during the stimulation showed concentration at 7.5 hours, or 3.5 hours after restoration of the pressure following removal of the stimulus This is evidence that the blood pressure may be maintained at shock levels for long periods by a purely nervous reflex vasodepressor mechanism, without serious impairment of either the vasomotor center in the medulla or the peripheral circulation and that the circulation may rapidly return to normal after stopping the stimulation It is additional support of the finding of Roome, Keith and Phemister that a sudden low blood pressure produced without local loss of circulating fluid impairs the circulation less and is better tolerated than an equally low blood pressure produced by such loss

In one animal the blood pressure starting at 106 mm Hg ranged between 55 and 80 mm Hg throughout the period of stimulation, and death did not occur until 13 hours had elapsed

In a small percentage of experiments the blood pressure was reduced to levels of 30 to 40 mm from the beginning, and there was usually a further gradual decline of pressure and a more rapid onset of failure of vasomotor tone, as indicated by poor recovery of blood pressure during temporary release of the stimulus Continued stimulation would result in a serious condition of the animal or in death in less time than in the preceding group Figure 3 shows an experiment in which the blood pressure fluctuated between 40 and 30 mm Hg during the first hour, and between 28 and 24 mm during the following one and one-half hours, when death occurred Vasomotor tone was greatly reduced after the first hour, as shown by brief releases of the stimulus then, and at the end of the second hour There was progressive hemodilution, as shown by the reductions in red count, hemoglobin, hematocrit and plasma proteins Arterial blood oxygen was considerably reduced and carbon dioxide strikingly so This was one of the most rapid deaths that was produced by very low blood pressure from cardio-aortic depressor nerve stimulation, and both the failing vasomotor tone and the progressive hemodilution with reduction of blood oxygen and carbon dioxide were responsible for it The cause of death in the animals dying with prolonged lowering of blood pressure to shock levels from nerve stimulation may well be designated as neurogenic shock Slight degenerative changes have been found in the parenchymatous organs of some of the animals

When the blood became considerably diluted and vasomotor tone showed signs of failure as a result of a long period of low blood pressure, produced by cardio-aortic nerve stimulation, the transfusion of either whole blood or plasma brought about a period of definite improvement of circulation The level of blood pressure during stimulation was elevated little or none, but the period of survival was prolonged, the response on release of the stimulus was improved, and the bleeding volume of the animal was approximately as great as that of controls Thus in one experiment the course was similar to that shown in Figure 3 and at the end of three hours the animal was almost moribund, with a blood pressure of 24 mm Hg, which rose to only 38 mm

on release of the stimulus. A blood transfusion of 20 per cent of the calculated blood volume, and 30-minute rest from stimulation, led to an elevation of blood pressure to 70 mm Hg, and the rabbit then lived for seven hours, despite three one-hour periods of stimulation and lowering of blood pressure in the meantime.

Figure 4 records an experiment in which an extremely low blood pressure in the vicinity of 30 mm Hg was maintained for four hours, with progres-

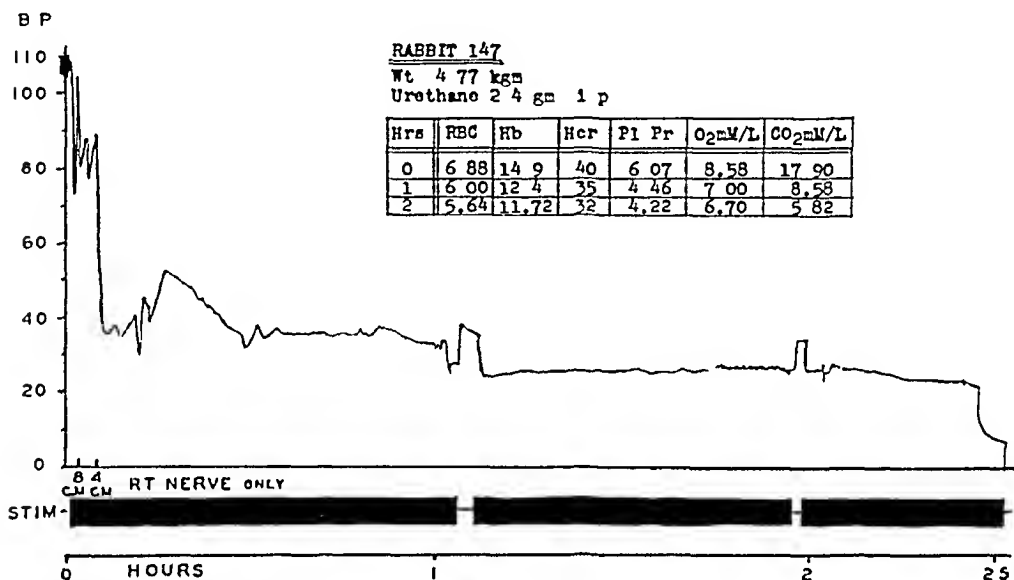


FIG 3—Marked and progressive vasodepression and early damage of vasomotor center with death in 2.5 hours. Progressive hemodilution and reduction of blood, oxygen and carbon dioxide.

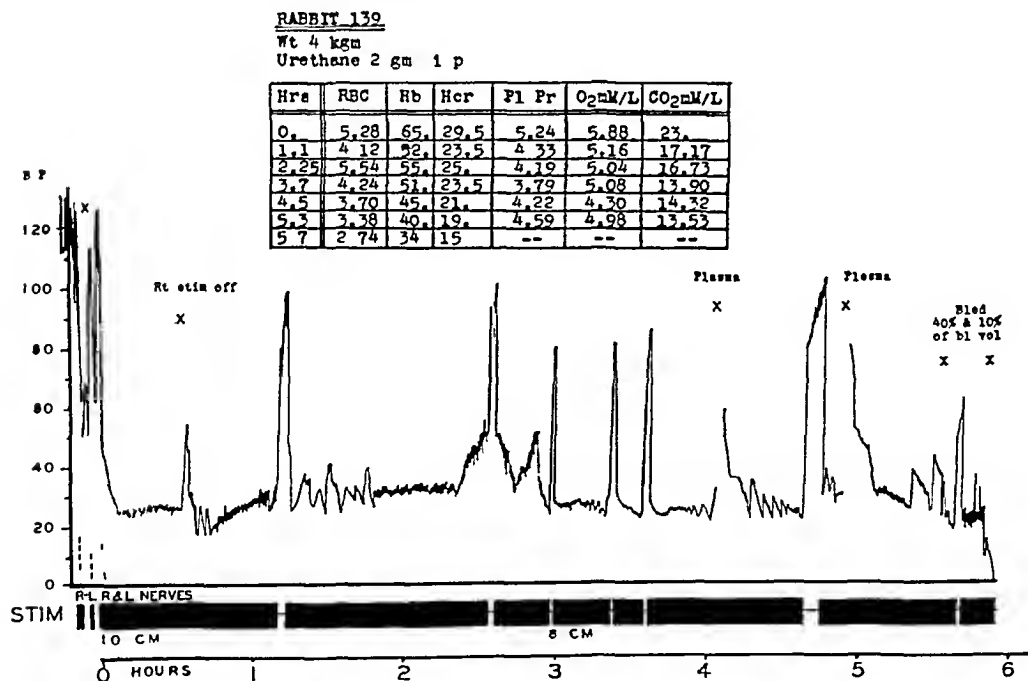


FIG 4—Marked lowering of blood pressure without exhaustion of vasomotor center for four hours. Plasma transfusions improved circulation. Large terminal bleeding volume.

sive hemodilution and blood oxygen and carbon dioxide reduction, but with only moderate decline of vasopressor response on release of the stimulus. A 27-cc plasma transfusion then raised the pressure only briefly, but release of the stimulus at 4.66 hours resulted in an increase in the level of elevation of blood pressure. A second 27-cc transfusion at five hours further improved the circulation, and at 5.66 hours the animal was bled 40 per cent of the calculated blood volume during stimulation. The pressure was only moderately reduced by the bleeding and, on release of the stimulus shortly afterward, it rose to 60 mm Hg, showing that the vasomotor center was still quite active. An additional ten per cent bleeding during stimulation was required to kill the animal. The plasma transfusions resulted in reductions in red counts and hemoglobin and hematocrit readings, but the increase in circulating volume and osmotic pressure prolonged life and improved the response of pressure on release of the vasodepressor stimulus.

Bleeding experiments were performed in order to test the effect of neurogenic lowering of blood pressure on animals that were already in a state of impending or actual shock as a result of hemorrhage. Clinically, severe hemorrhage followed by fainting, or by a fall of blood pressure from upper abdominal manipulation, might simulate the experiment. From 15 to 35 per cent of the calculated blood volume was withdrawn intermittently in a number of rabbits, reducing the blood pressure to 70 mm Hg, or below. After the lapse of 15 to 40 minutes, the cardio-aortic nerves were stimulated and the blood pressure was, thereby, reduced to considerably lower shock levels. Usually, this resulted in some shortening of the survival period, as compared with controls, but the difference was not very great. Figure 5 is the record of an experiment in which after testing the effects of cardio-aortic nerve stimulation, the animal was bled first ten per cent and then seven per cent of the calculated blood volume, which resulted in a blood pressure maintained at about 60 mm Hg 40 minutes later. Under stimulation, it was then maintained between 30 and 40 mm Hg for almost one hour before death occurred, with little pressor response on release of the stimulus shortly before. The blood which before showed slight dilution as a result of the hemorrhage, was concentrated near the end of the period of further depression under stimulation. It appears that the vasodepression from nerve stimulation shortened the survival time. However, in one case, when the blood loss was relatively small (15 per cent), the survival time, under further marked reduction of pressure by nerve stimulation, was remarkably long (seven hours).

In seven rabbits the effect on the circulation of lowering of blood pressure to levels averaging 40 to 50 mm Hg for periods of one to 4.33 hours by cardio-aortic nerve stimulation was tested by finding out how well bleeding was tolerated at the end of that time. It was found that the bleeding volume, which for seven controls averaged 42.5 per cent of the blood volume, estimated by the Evans blue dye method, varied from a moderate reduction to normal the average being 39 per cent. This showed that although the

RABBIT 107

Wt. 4.55 kgm.

Urethane 2.28 gm. i.p.

Hrs.	RBC	Hb.	Hcr.
0	6.68	87.7	44.8
1.1	6.44	86.2	41.2
2.3	7.54	99.0	46.1

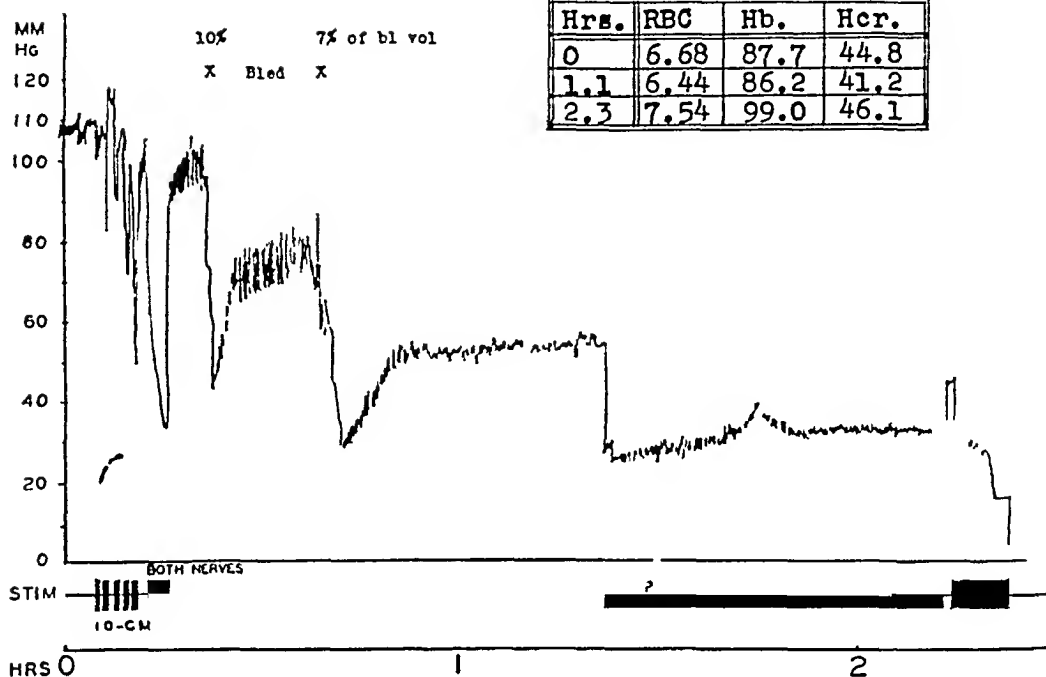


FIG 5—Shock produced by hemorrhage made worse by further lowering of blood pressure by aortic depressor nerve stimulation

DOG 161

Wt. 7.8 kgm.

Evipal 312 mgm.

Hrs.	RBC	Hcr.
0	7.28	32
13	5.26	32
25	6.40	36

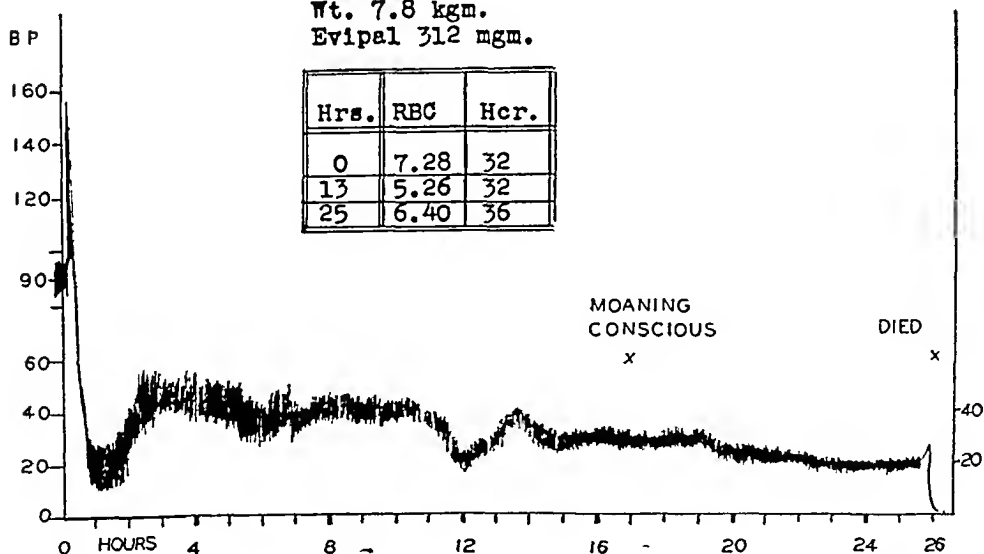


FIG 6—Section of spinal cord at C7, with maintenance of circulation at remarkably low level for 26 hours before death

pressure was at shock levels, the circulation was, on the whole, remarkably well preserved

The circulating blood volume during vasodepression was determined by Dr Paul Schaffer in five rabbits by the rather inaccurate Evans blue dye rapid method, drawing the five blood samples at ten minute intervals. The tests were made after two to three hours of stimulation and while the pressure was at shock levels. With the exception of the plasma protein in one experiment, a reduction in total volume, plasma volume and red cell mass was always obtained, the average being 17 per cent, 7 per cent and 34 per cent, respectively.

Further evidence that the blood pressure may be reduced to low shock levels for prolonged periods of time by a neurogenic mechanism before there is failure of the circulation has been obtained by the study of nine dogs with section of the lower cervical portion of the spinal cord. Under intravenous evipal anesthesia, 40 mg per Kg body weight, the femoral arteries were cannulated. One was used for drawing blood samples while the blood pressure was recorded continuously from the other. The spinal cord was then cut, aseptically, at the level of C-8 interrupting the sympathetic pathways from the vasomotor center in the medulla to the blood vessels and heart, and the animal followed until death. The stimulus of cutting the cord causes a brief rise in blood pressure and tachycardia which are followed by a sustained fall in blood pressure and bradycardia. Under the conditions of this experiment, the animals, with one exception, regained consciousness and remained in a quiet state of depression until coma supervened. The blood pressure varied with the experiment, but ranged between 70 and 20 mm Hg, usually declining slowly until death took place in 25 to 33 hours. During the first 15 to 20 hours, the blood underwent dilution, after which it usually concentrated. Hemorrhage into the small intestine was usually found at autopsy, similar to that observed by Blalock¹³ in dogs dying of shock produced by slow hemorrhage. Figure 6 records the findings in an animal in which the blood pressure dropped to the unusually low level of 20 mm Hg during the second hour, to recover to 50 mm Hg by the third hour, and then slowly declined to 20 mm again, with death in 26 hours. The pulse rate varied between 90 and 60 per minute. Despite the low blood pressure, the animal remained partly conscious and occasionally moaned for 16 hours. The red cell counts showed a hemodilution during the first half of the experiment followed by hemoconcentration. The discrepancy in hematocrit readings is unexplained but may have been due to swelling of the red cells.

SUMMARY AND CONCLUSIONS

Neurogenic shock was produced by prolonged electrical stimulation of the cardio-aortic (aortic depressor) nerves of the rabbit resulting in marked and prolonged lowering of blood pressure, hemodilution anoxia and terminal exhaustion of the vasomotor center of the medulla. Usually there was a lapse of four to seven hours before serious impairment of the vasomotor

center and of five to eight hours before death. Removal of the stimulus before serious impairment of the center was followed by rapid recovery of the circulation. In exceptional experiments, the blood pressure was maintained at very low levels and the course was more rapid. The results serve as an index of the effect of hyperactivity of afferent vaso depressor impulses which would be the same regardless of the pathways over which they came to the medulla. The possibility that shock is ever produced by accidental injury of the cardio aortic nerves is so small that it scarcely merits consideration. Blood and plasma transfusions improved the condition of the shocked animals.

In dogs with section of the seventh cervical segment of the spinal cord, a remarkably severe and prolonged lowering of blood pressure resulted before there was failure of the circulation and death. These results demonstrate the marked capacity of the circulation to remain adequate when the blood pressure is lowered, principally by interference with vasoconstrictor nerve impulses to the blood vessels with relatively little associated blood loss.

Nothing remotely approaching this degree and duration of lowered blood pressure and failure of the circulation has been produced by direct stimulation of the somatic nerves. Consequently, it is highly improbable in accidental and operative wounds that shock ever results primarily, or even secondarily, from the action of afferent vasodepressor impulses passing over the somatic nerves that are injured in the field.

Vasomotor and cardiac afferent depressor impulses from the brain to the medullary center may lower blood pressure and produce syncope but they act for too short a time to be the sole cause of shock in comparison with the long time required for its experimental production from an equally marked lowering of pressure by aortic depressor nerve stimulation. The same is true of the occasional reflex lowering of pressure in abdominal operations. However, when combined with hemorrhage, these may be contributing factors in shock production as were vasodepressor impulses from cardio-aortic nerve stimulation when preceded by hemorrhage to shock levels in these experiments.

A fuller realization on the part of the surgeon of the relatively small importance of hyperactivity of afferent depressor nerve impulses and of the relatively great importance of blood and plasma loss and toxicity of anesthetics in the causation of surgical shock will lead to greater attention to the latter factors and to further improvement in surgical therapy. The primary cause of shock is probably never a purely reflex vasodepressor reaction.

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DISCUSSION—DR. ALFRED BLALOCK (Baltimore) These are two excellent papers Dr Phemister and I, and others, have maintained for a good many years that the most important agency in the initiation of traumatic shock is the regional loss of fluid from the blood stream Most of the pathologists and the physiologists have maintained that there is a general increase in capillary permeability even in the early stages of shock

Now Doctor Fine and his group, Gregersen and Root, at Columbia, Gibson and Aub, in Boston, Evans, of Richmond and others, have come to the conclusion that there is not a general increase in capillary permeability in traumatic shock even in the terminal stages Even though I can find no flaw in their experiments, it is difficult for me to accept this whole-heartedly It would appear that in the terminal stages there should be a general increase in capillary permeability, but, as I say, the evidence points in the other direction

I hope that Doctor Fine, and others, are correct in their findings, because it makes for a more hopeful outlook in therapy Certainly, the inability to establish any definite beneficial effect from the use of adrenal cortical extract would indicate that they are correct

Perhaps several remarks regarding the three prevailing theories on traumatic shock would not be out of order, namely, the regional fluid loss, the nervous influences, and the toxemia theory

First, as regards the regional loss of fluid, I would agree with what Doctor Phemister said in his introduction The importance of this in most cases of shock has been established and the beneficial effects of the use of blood and blood substitutes have been shown It would appear that further study along this line should be in connection with the finding of other blood substitutes, such as perhaps Doctor Lockwood will talk about this morning

Secondly as regards the rôle of the nervous system in shock, this has been covered by Doctor Phemister It would appear that studies along this line would not be extremely hopeful as making for better therapy At least it seems that attempts to block nerves have not resulted in much benefit in the treatment of traumatic shock Certainly, the use of spinal anesthesia is not advised in the treatment of traumatic shock due to injuries to the lower extremities so it would appear that further researches along this line would not be particularly hopeful This is not saying that the nervous system has nothing to do with the genesis of traumatic shock

Thirdly, as regards the so-called toxemia theory, or what perhaps today had

better be spoken of in terms of metabolic disturbance, perhaps the future outlook is somewhat better, for it does appear very likely that there are chemical hormonal disturbances that might be treated successfully

The results of Doctor Fine in this connection are exceedingly interesting, as are those of C N H Long, of Prinzmetal, and of many other investigators

In other words, as Doctor Pharmister has said, it appears that the regional fluid loss factor is now fairly generally appreciated, and one can use blood and blood substitutes and other agencies, such as Doctor Elman spoke of yesterday, to correct this condition. At least from the experimental viewpoint it would appear to me that our energies should now be directed toward this third point, whether it be a toxemia or whether it be the chemical disturbances, and try to find an accessory means of improving our present knowledge on the treatment of this condition

Again I want to say how much I enjoyed these two excellent papers, and they represent the work of two groups out of approximately forty-five different groups in this country who are studying shock

DR JACOB FINE (closing) It is difficult to find one's way in the literature on shock because of contradictory evidence from equally competent investigators. These contradictions are frequently due to differences in the experimental conditions, the significance of which often are not sufficiently evaluated. The literature on tourniquet shock, in particular, is a good example. Nearly all the recent studies on this type of shock indicate that recovery is seldom achieved even with large transfusions of plasma or other blood substitutes. Our own experience, however, is that recovery from tourniquet shock is the usual result from the transfusion of plasma or other blood substitutes. The reason for this difference in the result is that in our dogs no anesthesia, except morphine, was used, while barbiturate anesthesia, which is known to be capable of aggravating the state of shock, has been uniformly used by other investigators. Thus, Milon and Winternitz (Am Jour Phys, June, 1943), using nembutalized dogs, found that tourniquet shock (tourniquets to both hind limbs for five hours) if untreated, is uniformly fatal. When we produced this type of tourniquet shock (i.e., tourniquets for five hours to both hind limbs) using morphine alone, the dogs commonly failed to go into shock. When they treated such dogs with plasma albumin no beneficial effect was obtained, but cure was achieved with sodium succinate and saline solution. The cure achieved by sodium succinate and saline solution may well have been due to the neutralizing by succinate of the effect of nembutal on tissue respiration, thus permitting spontaneous recovery, as in our own unanesthetized dogs. The fact that their dogs, if untreated, uniformly died does not mean that tourniquet shock (for five hours to both hind limbs) is uniformly fatal. It does mean that this type of tourniquet shock *plus nembutal anesthesia* is uniformly fatal.

DR. DALLAS B PHARMISTER (closing) I only want to say that one of the ideas that should be gotten out of the head of the average member of the medical profession is the traditional fixed one that shock may be produced by afferent vaso-depressor nerve influences. I am not discussing other neurogenic theories.

SURGICAL GUT (CATGUT) TUBING FLUID AS A TISSUE IRRITANT*

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IN AN extensive study of the absorption of surgical gut (catgut), recently published by Jenkins and coworkers¹ a point of considerable interest was the noticeable variation in the magnitude of the tissue reaction which was observed in tissue implantation tests of surgical gut products from different commercial sources. Those products which had a tendency to produce the more conspicuous tissue reactions were usually observed to undergo a more rapid loss of tensile strength and frequently a more rapid rate of complete absorption than products which produced a less conspicuous tissue reaction. Relatively rapid absorption was generally found to be associated with a predominantly leukocytic reaction, to which the gut appeared to be especially vulnerable. Relatively slow absorption was associated with a predominantly macrophage response which appeared after an initial leukocytic invasion of varying magnitude which in some instances was relatively negligible. Although it was generally found that the surgical gut from certain sources tended to produce conspicuous reactions while minimal reactions were observed with products from other sources, there were many exceptions encountered.

On the basis of the observations made, there appeared to be some unexplained factor which contributed to the magnitude of the tissue reactions observed. This factor was not apparently an inherent property of the gut *per se* because it was not constant in all products. This prompted us to explore the possibilities of the presence of a tissue irritant in the tubing fluids commonly used for surgical gut, which, if carried into the tissues along with the gut, could explain many of the reactions observed. This study concerns itself with the two general classes of tubing fluids, namely, the anhydrous liquids used for boilable gut, and the alcoholic solutions used for the non-boilable surgical gut.

BOILABLE PRODUCTS

Many manufacturers have used xylene (xylol) as a tubing fluid for their boilable products because this is a completely anhydrous liquid and does not cause any damage to the gut when the tubes are subjected to boiling or autoclaving for surface sterilization of the glass before use in the operating room. Furthermore, the manufacturers can heat-sterilize the surgical gut after sealing.

*Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

the tubes if they use an anhydrous liquid such as xylene. Some manufacturers have, at one time or another, used toluene (toluol) instead of xylene.

EXPERIMENTS

1 An intradermal injection of 0.025 cc of xylene tubing fluid, obtained from a commonly used boilable product, was made in the skin of the forearm of one of us. Within six hours there was a red, tender welt, 0.5 cm high and 4.0 cm in diameter, at the site of the injection. The reaction was extremely painful and subsided over a period of one week. There was no superficial necrosis. The lesion resembled an acute cellulitis such as one sees produced by streptococcus infections.

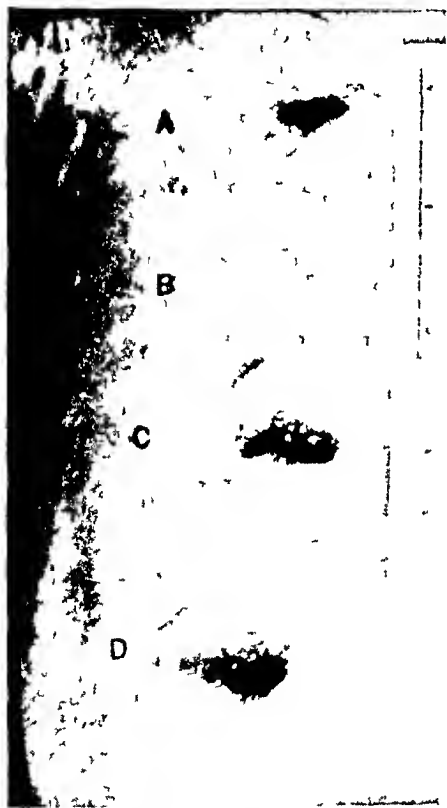


FIG 1—Showing tissue necrosis 48 hours after intradermal injection of 0.05 cc amounts of (A) xylene (A C S), (B) Toluene (A C S), (C) xylene tubing fluid, and (D) hi flash solvent, into the back of a dog. Ulceration of the necrotic skin has occurred in all except the toluene injection.

2 Intradermal tests were carried out on a series of animals using 0.05 cc of xylene (A C S), toluene (A C S), and xylene which had been used as a tubing fluid for surgical gut. In a few experiments white rats and rabbits were used, but it was found that the skin of the back of dogs, being less delicate, was more satisfactory for this work. The immediate reactions to the injections were relatively slight. By the end of an hour one could see only a pale, slightly elevated wheal 1 to 2 cm in diameter, but by the end of 18 hours permanent tissue damage had occurred. The xylene (A C S) regularly produced necrotic lesions 1 to 2 cm in diameter surrounded by an edematous and reddened inflammatory margin several millimeters wide. Xylene tubing fluid appeared to produce somewhat more conspicuous lesions than standard laboratory xylene (A C S). Sloughing of the necrotic areas followed in a few days. Toluene (A C S) produced less severe reactions and in most instances these were ultimately not much greater in magnitude than those described below as

characteristic of 95% ethyl alcohol (Fig 1).

3 Intradermal tests were carried out in dogs using 0.05 cc of varying concentrations of xylene and toluene (1, 5, 10, 15 and 50 per cent by volume) in 95% ethyl alcohol. Control injections using 95% ethyl alcohol produced an immediate coagulation of the tissues, surrounded by erythema. The lesions did not progress and the erythema tended to subside rapidly. These lesions rarely exceeded 1 cm in diameter and were usually 0.5 cm or less, their size

being determined largely by variations in the technic of injection, especially the depth of penetration of the needle. The more superficial the injection the greater the tendency to spreading, with the result that the lesion produced would have a greater diameter. It should be mentioned here that the same amount of alcohol (0.05 cc) injected into the human skin usually produced only relatively transient lesions which were negligible after a day or two. The mixtures of xylene and toluene in alcohol characteristically produced an immediate coagulation of the tissues at the site of injection, with the development progressively of erythema and appreciable necrosis for the higher concentrations of the solvents in alcohol. Injections of 50% xylene and 50% toluene in alcohol produced lesions which were of a greater magnitude than were observed with undiluted xylene or toluene, respectively. The mixtures with lower concentrations of xylene or toluene in alcohol produced lesions somewhat more striking than the alcohol controls, the magnitude varying in proportion to the concentration of xylene or toluene.

NONBOILABLE PRODUCTS

The tubing fluids used for nonboilable surgical gut have been alcoholic solutions, usually 95% or 96% ethyl alcohol plus a small amount of some germicidal agent. The compositions of the tubing fluids of the various manufacturers may vary to some extent from time to time. In recent years the following formulae have been used:

Ethyl alcohol 95%, with phenyl mercuric benzoate 0.02% or potassium mercuric iodide 0.3% or 0.1%

Ethyl alcohol 96%, with phenyl mercuric benzoate 0.1% or potassium mercuric iodide 0.2%

Ethyl alcohol 76% and isopropyl alcohol 20%, with potassium mercuric iodide 0.06%

Alcohol, anhydrous and methanol 3% to 14% and in certain products 0.8% to 2.5% iodide

The alcoholic solution which contains 4 to 5% of water renders the surgical gut pliable, so that it can be used for suturing as soon as the tube is opened without having to resort to the wetting procedures required for rendering boilable products pliable. In one product anhydrous alcohol was used with varying amounts of methanol. The presence of the latter apparently induces pliability in the absence of water. These alcoholic solutions seriously damage the gut if the tubes are heated and, therefore, it is necessary to surface sterilize the glass by chemical agents instead of by boiling or autoclaving. The sterility standard of the gut within the tubes is fundamentally the same for nonboilable products as for the boilable, because extensive heat sterilization has been carried out in an anhydrous liquid just as is done for boilable gut. The liquid used for heat sterilizing is then removed to a greater or less extent from the tubes, the alcoholic solution is added and the tubes sealed.

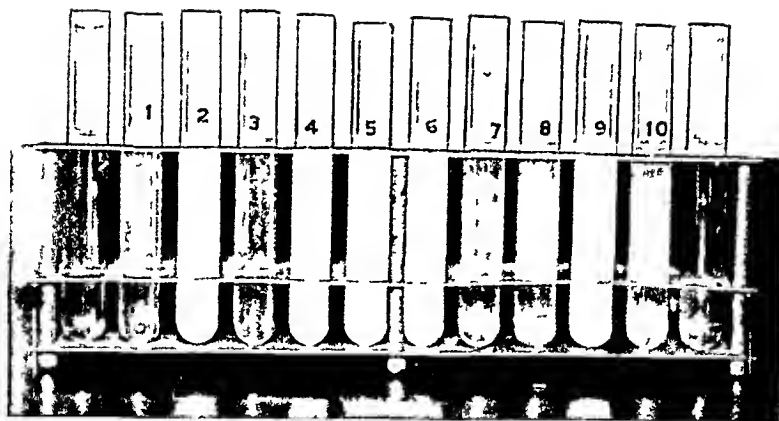


FIG 2—Showing the "emulsion test" on nonboilable surgical gut tubing fluid of ten different companies. To 0.5 cc of alcoholic tubing fluid 5 cc of water were added. Definite evidence of emulsion is shown for Companies II, IV, V, VI, and IX. A very slight clouding suggestive of a trace of water insoluble component is shown for Companies I, VII, VIII, and X. The tube for Company III is practically as clear as the alcohol water controls at each end of the rack (tubes without number).

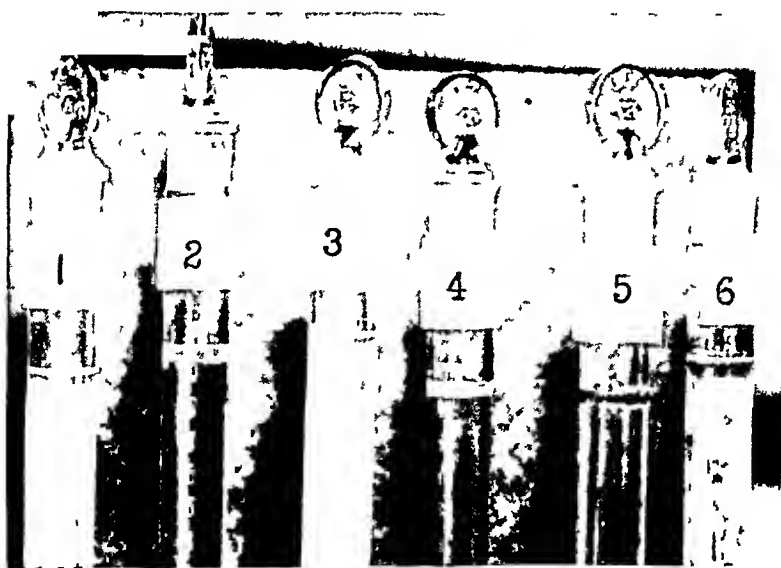


FIG 3—Showing supernatant water insoluble liquid obtained from the alcoholic tubing fluid of the nonboilable surgical gut of six different companies. To 10 cc of tubing fluid in 100 cc cassia flasks (lower bulbous portion of flask not shown) water was added to produce emulsion and this was acidified with concentrated H_2SO_4 to expedite separation of water insoluble component the amount of which could then be read off as tenths of a cubic centimeter in the graduated neck of the flask, each tenth of a cubic centimeter representing 1%. In this test there was 4 to 15% of water insoluble liquid recovered from four of the products, while in two products none was obtained.

EXPERIMENTS

4 During the course of the previously mentioned study of the absorption of surgical gut¹ it was noticed that certain of the alcoholic tubing fluids became white upon the addition of water. The full significance of this observation was not appreciated at the time. Subsequent examination under the microscope of the white fluid produced by the addition of water to the alcoholic tubing fluid revealed minute globules of varying size which exhibited characteristic brownian movement. It was obvious, therefore, that we were dealing with an emulsion produced when the alcoholic solution was diluted with water, thus revealing the presence in the alcoholic solution of a water-insoluble liquid component. The presence of such a component has not been mentioned by the manufacturers on the package labels.

A simple test was devised for determining whether appreciable quantities of this water-insoluble component were present in the alcoholic tubing fluid. The addition of 5 cc of distilled water to 0.5 cc of tubing fluid produced a creamy emulsion when there was much of this material present. This was considered a positive test. If the solution remained clear it was considered negative. If a slight turbidity appeared it was considered as indicating a trace of water-insoluble liquid. A number of tests were run on samples of tubing fluids from the products of ten different manufacturers. The tubing fluids of five of these companies gave strongly positive reactions to this test (Fig. 2).

5 We next attempted to separate the water-insoluble component from the rest of the tubing fluid in order to get a rough idea of how much of it was present. We were able to do this by acidification. Ten cubic centimeters of tubing fluid from each of six different companies was placed in separate cassia flasks and diluted with 85 cc of distilled water. Five cubic centimeters of concentrated sulphuric acid was then added, and the flasks securely stoppered and shaken. A conspicuous emulsion appeared in four of the six flasks, while the fluid in the other two remained only slightly turbid. At the end of a few days the water-insoluble material had collected as a supernatant layer in the graduated necks of the four flasks which had contained the heavy emulsion. The amount of supernatant liquid varied from 0.4 cc to 1.5 cc. This would indicate concentrations of water-insoluble material in the alcoholic tubing fluids of from 40 to 150 per cent in these four products (Fig. 3).

6 The cooperation of an independent chemical laboratory was obtained in an endeavor to get more exact information about the nature and amount of this water-insoluble component which we had found in certain of the alcoholic tubing fluids. The report of this phase of the work will be made independently by Albert E. Sidwell, Jr. (*ANNALS OF SURGERY*, 118, 285, August, 1943).

We obtained from this source specimens of the water-insoluble components which had been recovered by fractional distillation. The relatively high boiling range of these materials (140° to 190° C) was of particular interest. This material was used by us in subsequent experiments for titration and intradermal tests.

7 The "emulsion titration test" was devised to obtain some quantitative data on the water-insoluble component in the alcoholic tubing fluid of individual tubes of nonboilable surgical gut. This is based upon the saturation point of water-alcohol mixtures for water-insoluble liquids which are soluble in alcohol. This consists of titrating two cubic centimeters of alcoholic tubing fluid with distilled water. The end-point is considered to have been reached when a persistent cloudiness from the emulsion occurs. The amount of

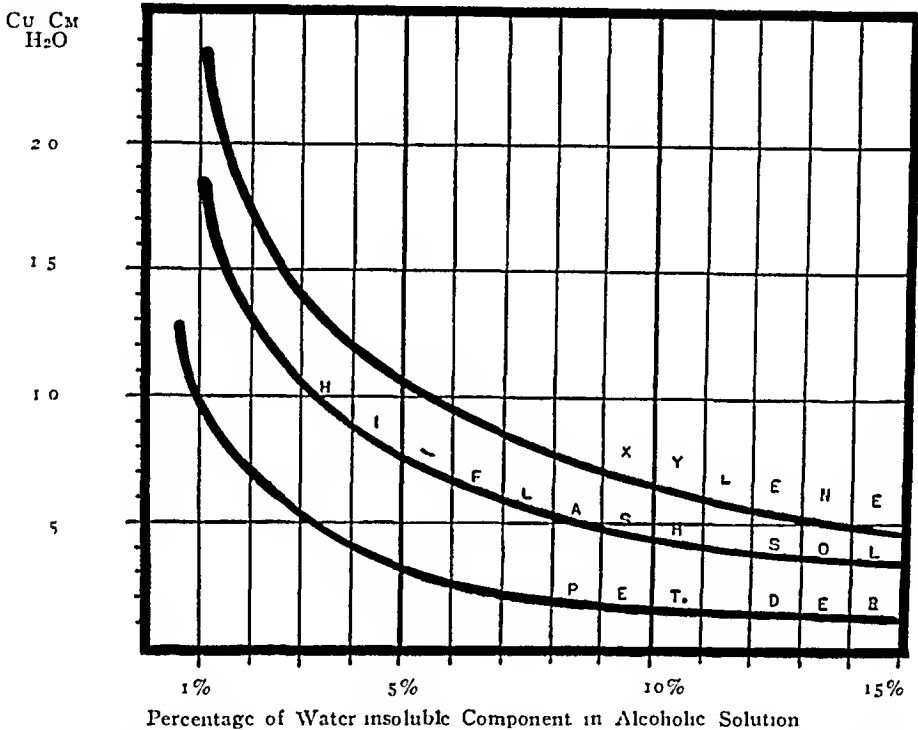


FIG 4—Showing solubility of xylene, hi flash solvent and a petroleum derivative in varying water—alcohol mixtures. The curves were derived from saturation points of different concentrations of these solvents in various water—alcohol mixtures expressed in terms of the number of cubic centimeters of distilled water which must be added to the various concentrations of these solvents in 95% alcohol to produce emulsion. The curve for hi flash solvent is practically superimposable on that for the high boiling point distillate recovered from alcoholic tubing fluid (Table I).

water required to produce the emulsion must then be interpreted from a graph prepared by titrating known concentrations of the water insoluble liquid in alcohol such as is demonstrated in Figure 4. The interpretation of the amount of water-insoluble component present depends, therefore, on the nature of the water-insoluble liquid (Table I). The curve for hi-flash solvent* obtained by titrating known amounts in alcohol was found to be practically superimposable on that for the high boiling range fraction which was isolated by Sidwell from pooled alcoholic tubing fluid of recent manufacture. Therefore, the results of the titrations in terms of distilled water may then be interpolated into per cent of hi-flash solvent in the fluid (Table II). These results cannot be construed as representing quantitative analyses, but rather an approximation of the water-insoluble component be-

* Hi-flash solvent, boiling range 163° C to 180° C, an anhydrous hydrocarbon coal tar derivative supplied to manufacturers for the purpose of heat sterilization of catgut

SURGICAL CATGUT TUBING FLUID

lieved to be present These results, however, have been comparable to the emulsion separation tests as well as to the results described by Sidwell Over 175 tubes of nonboilable catgut were subjected to this "emulsion titration test"

TABLE I
Cc H₂O Required for Titration to Produce Emulsion

% Solvent in Alcohol	Toluene	Xylene	T F Dist	Hi-flash	Pet Der
1	*	2 35	1 92	1 66	0 93
2 5	2 4	1 5	1 12	1 13	0 51
5	1 6	1 05	0 68	0 76	0 30
10	1 0	0 65	0 45	0 42	0 15
15	0 65	0 45	0 35	0 31	

Emulsion Titration Test Titrations with distilled water of 2 cc aliquots of various concentrations in 95% ethyl alcohol C P of toluene xylene pooled tubing fluid distillate, hi-flash solvent and the petroleum derivative

TABLE II
AMOUNT OF WATER REQUIRED TO PRODUCE EMULSION IN 2 CC OF ALCOHOLIC TUBING FLUID AND THE INTERPRETATION OF THESE RESULTS IN TERMS OF PERCENTAGE OF WATER-INSOLUBLE COMPONENT (W I C)

Company	Series 1941-42		Series 1939-40		Series 1938	
	H ₂ O	W I C	H ₂ O	W I C	H ₂ O	W I C
I	1 32 cc	2 0%	1 5 cc	1 5%	2*	Trace
	2*	Trace	2*	Trace	2*	Trace
II	62 cc	6 5%	45 cc	10%	44 cc	10%
	91 cc	4 0%	2* cc	Trace	2* cc	Trace
III	1 1 cc	3%	63 cc	6 5%	82 cc	4 5%
	2* cc	Trace	2* cc	Trace	2 1 cc	Trace
IV	91 cc	4%	21 cc	7 0%	23 cc	6 5%
	1 42 cc	1 5%	64 cc	2 25%	87 cc	1 2%
V	47 cc	9 5%	52 cc	8%	64 cc	6%
	2 * cc	Trace	2* cc	Trace	2 * cc	Trace
VI	35 cc	14%	24 cc	?	2 cc	?
	71 cc	6%	50 cc	?	47 cc	?

*2 means 2 cc or more of water

The W I C was interpreted from the graph in Fig 4 using the curve which was characteristic of hi-flash solvent because the solubility curve of the water insoluble component recovered from most products closely resembled that of hi-flash solvent

In one product the results of the titration test were interpreted in terms of petroleum derivative, which was believed to be the water-insoluble liquid during certain years

In another product the titration tests were not evaluated for past years because data on the nature of the water insoluble component was not available

The "Emulsion Titration Tests" showed that over a considerable period of time there has been an appreciable amount of water-insoluble liquid present in alcoholic tubing fluid of most nonboilable surgical gut products This has ranged from a trace to up as high as 10% in some products, while in one product it ranged from 6 to 14% In some instances it ranged from a trace to 6%, or a trace up to 2% There was considerable variation in tests made on the same product, as well as on different tubes in the same package lot It was of interest to find that in one series of tests on one product, all tests showed not more than a trace, while in a subsequent series on this product, 12 out of 15 tests showed only a trace

8 Injection experiments were devised to ascertain whether the water-insoluble liquid found in the alcoholic tubing fluids of nonboilable products

was irritating to the tissues. Intradermal injections of 0.05 cc. of the alcoholic tubing fluids of six different manufacturers were made in the backs of three human subjects. Control injections were made with 95% ethyl alcohol. The alcohol injections produced an immediate whitening of the tissues at the site of injection. This was from 3 to 5 mm. in diameter. About it there developed, in a matter of minutes, a wheal 1.0 to 1.5 cm. in diameter surrounded, in turn, by an erythematous flare approximately 2 cm. across. This reaction reached



FIG. 5.—Showing irritant action of alcoholic tubing fluids of six different nonboilable products as compared with 95% ethyl alcohol by intradermal tests (0.05 cc.) in Subject J after 24 hours. Maximum reaction was observed for Companies II, V and VI. Moderate reaction was seen for Company IV, and slight reactions for Companies I and III. The least reactions were obtained with 95% ethyl alcohol controls. Compare the magnitude of the tissue reaction here with the amount of water insoluble component demonstrated in Figures 2 and 3, for the several products tested.

its maximum in one-half hour and then gradually subsided over a period of several hours. In many of the tests there was only slight evidence of reaction after 24 hours, although in one test there was produced a small area of necrosis, 2-3 mm. across, which subsequently ulcerated. In contrast to the action of pure alcohol, the alcoholic tubing fluids produced immediate reactions similar in character to the above but of a greater magnitude, and at the end of 24 hours they had all produced lesions in which the central white area persisted and, regularly, lead to actual necrosis and subsequent ulceration. Furthermore, the surrounding tissues for a matter of several millimeters to more than a centimeter were red and inflamed (Figs. 5 and 6). A comparison of Figure 6 with Figure 2 and Table II brings out rather strikingly the tendency for those tubing fluids which contained an abundance of water-insoluble component to produce the largest skin reactions. In some instances the lesions after undergoing ulceration required more than a month to heal over.

9 The pooled high boiling point distillate referred to above (Experi 7) was also used for intradermal injections Five-hundredths of one cubic centimeter of this material in concentrations of 1, 5, 10 and 15 per cent in 95% ethyl alcohol was injected into the skin of the back of a human subject

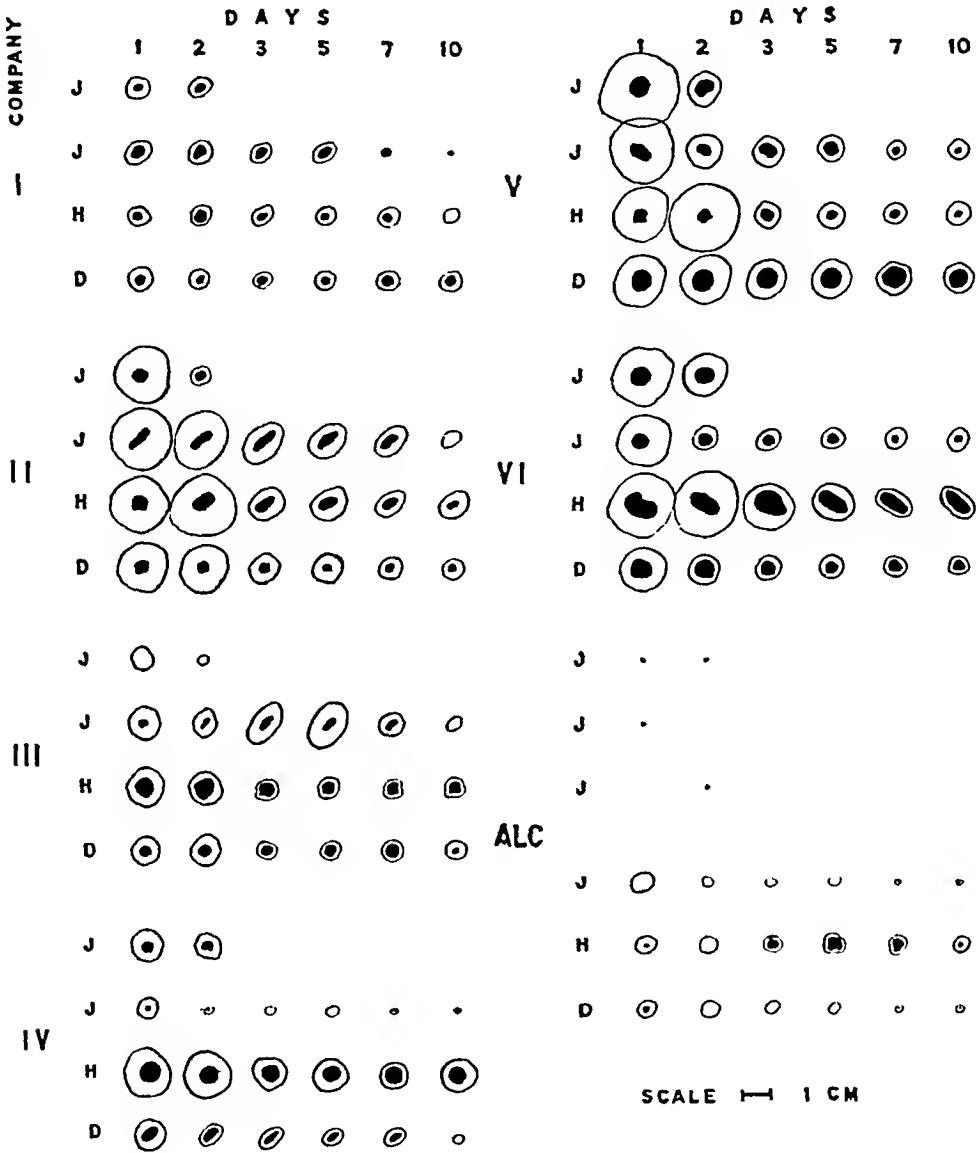


FIG. 6—Scale drawing showing the variation in the tissue reaction obtained by intradermal injection (0.05 cc) of various alcoholic tubing fluids and pure 95% alcohol from one to ten days after injection. The skin of the back of three human subjects was used. The alcoholic tubing fluids were obtained from the nonboilable surgical gut of six different manufacturers, indicated as Companies I, II, etc. The area within the circle represents erythema, the solid black center represents necrosis. The alcoholic tubing fluids of Companies II, V, and VI, appeared to be the most irritating while those of Companies IV, III, and I, were less irritating. All of these alcoholic tubing fluids were more irritating than pure 95% alcohol. The magnitude of the tissue reaction appears to correlate with the amount of water insoluble component present in these products as demonstrated in Figures 2 and 3.

The magnitude of central necrosis and peripheral inflammatory reaction varied in proportion to the amount of distillate present. The alcohol produced a minimal lesion which had almost subsided on the day after injection. The higher concentrations produced lesions which required several weeks to heal. Concentrations as low as one per cent of this high boiling range fraction of alcoholic tubing fluids are definitely necrosing in alcoholic solution. The

lesions produced were similar in all respects to those produced by the alcoholic tubing fluids themselves (Fig 7)

10 Similar intradermal tests were performed upon dogs, using small amounts (0.025 to 0.05 cc) of undiluted high boiling range distillates recov-

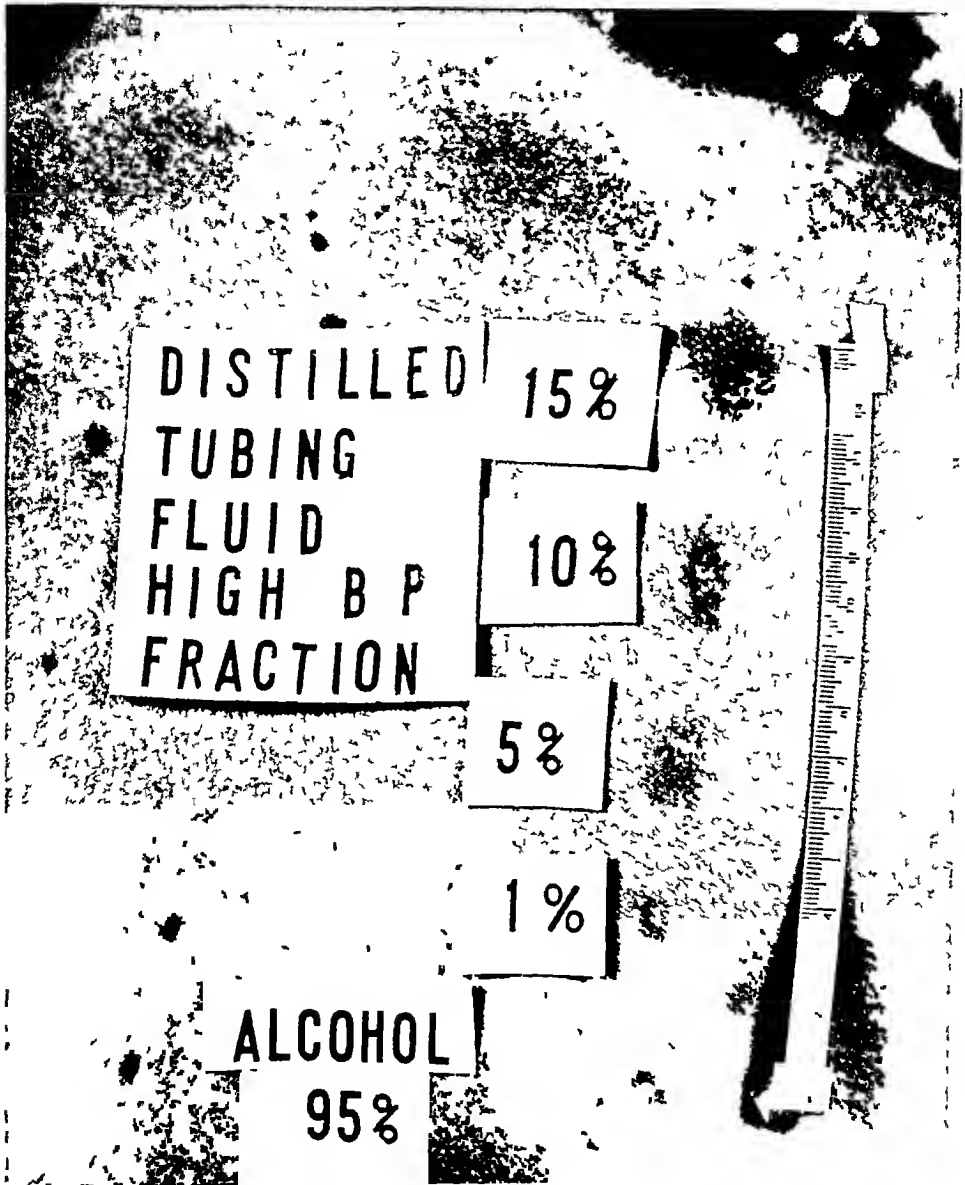


FIG 7—Showing intradermal tests (0.05 cc) on Subject J, at 24 hours, using known concentrations in 95 per cent ethyl alcohol of a mixture of high boiling range (140° – 160° C) water insoluble material obtained by distillation of nonboilable alcoholic tubing fluids. In concentrations as low as one per cent, this water insoluble liquid produces irritation of a greater magnitude (erythema and necrosis) than the 95 per cent ethyl alcohol control (erythema which has almost subsided). The lesions produced by the 5, 10, and 15 per cent concentrations compare with those in Figure 5

ered separately from five products. All five distillates produced necrotic lesions, approximately 2 cm in diameter, which subsequently sloughed and ulcerated. The immediate reactions resembled those characteristic of xylene, and it was not until the following day that the potent necrosing action of the

materials was apparent. There was no appreciable difference in the magnitude of the reaction produced by the distillates from the five different products. They all appeared to be somewhat more potent irritants and necrosing agents than xylene.

11 Intradermal tests were performed upon dogs with undiluted hi-flash solvent and with the material referred to in Experiment 7 as petroleum derivative, and which was believed to represent the water-insoluble component present in the tubing fluid during certain years of at least one brand of non-boilable gut. Hi-flash solvent behaved exactly like the undiluted distillates used in Experiment 10, producing on the second day large necrotic lesions which subsequently sloughed and ulcerated. The petroleum derivative produced the same end-result, the only difference noted being a hemorrhagic appearance of the necrotic area prior to its breakdown. Both of these solvents appeared to be more damaging to tissues than xylene tubing fluid.

Tests with various concentrations of these materials in 95% alcohol were also made on dogs. Hi-flash solvent was used in concentrations of 1, 5, 10, 15 and 50 per cent, while the petroleum derivative, which is not freely soluble up to 50 per cent in alcohol, was used in concentrations of 1, 5, 10, 15 and 25 per cent. Hi-flash solvent, 50% in alcohol, and petroleum derivative, 25% in alcohol, produced lesions of a definitely greater magnitude than when undiluted. In these experiments upon dogs' skin, which is much more susceptible to the action of 95% alcohol than is human skin (Exper 3), it was sometimes difficult to distinguish the lesions produced by the 1 and 5% concentrations from those produced by the alcohol controls. The 10 and 15% concentrations, however, produced lesions obviously greater than those produced by 95% alcohol.

12 Intradermal injections were made in dogs using varying concentrations of the germicidal agents used by manufacturers for their alcoholic tubing fluids. The lesions produced were difficult to distinguish from pure 95% alcohol controls. Phenyl mercuric benzoate is quite insoluble in water and therefore, could not be tested in aqueous solution. Tests using potassium mercuric iodide, 0.3% in saline, produced a relatively small area of edema in the skin of rabbits but no evidence of necrosis was obtained. These tests do not exclude the germicidal agents as a source of some irritant action in the tissues. Such action, if any, however, is negligible in comparison with that of the potent tissue irritants, hi-flash solvent, or xylene.

COMMENT

BOILABLE TUBING FLUID—The data from Exper 1 and 2 shows that xylene is a potent tissue irritant and in some tissues a necrosing agent. Furthermore, xylene from the tubing fluid of boilable gut appeared to be more of an irritant to tissues than xylene (A C S). This latter point raises the question as to whether the xylene used for the tubing fluid may not have been a commercial grade which contained additional irritants not present in the A C S grade. Another possibility is that some irritant material from

the gut may have been extracted by the xylene which enhanced its irritant property

It is surprising that no one has questioned the practice of using a liquid with known irritant properties as tubing fluid for surgical gut. In the experimental laboratory one of the commonest uses of xylene as an irritant is to produce vasodilation of the marginal ear vein of the rabbit in order to facilitate venepuncture. Xylene has been used to produce sterile inflammation by such students of tissue reactions as Rigdon,² and Hudack and McMaster.³ Steiner⁴ has used xylene in the tissues of experimental animals and found extensive tissue reactions as well as necrosis.

After a tube of boilable gut is opened it is necessary to render the gut sufficiently pliable for surgical use, because in a completely anhydrous state it is brittle and stiff. The procedure commonly recommended for accomplishing this is immersion for a few minutes in warm water or saline or wrapping it in a moist towel. Xylene is insoluble in water and the procedure designed primarily for softening the gut could not be expected to remove all the xylene. This can easily be demonstrated by the obvious smell of xylene remaining after a piece of gut has been softened in water. Manufacturers have not pointed out the desirability of eliminating the liquid which was used as a tubing fluid nor have they called attention to its irritant properties. Certainly if the xylene tubing fluid is not eliminated from boilable surgical gut before it is introduced into the tissue one should not be surprised to find in the wound a tissue reaction due in large part to the xylene left in and on the gut rather than to any inherent properties of the suture material itself.

It is customary in some operating rooms to render boilable gut pliable by immersion in 70% alcohol. This requires a longer period of time for obtaining the desired pliability than is necessary with warm water or saline, but it has the advantage of removing to a greater extent the xylene tubing fluid. Seventy per cent alcohol is not a satisfactory agent for complete removal of xylene, however, because xylene is not as freely soluble in this concentration of alcohol. Ninety-five per cent alcohol could be used but would require a longer period of time as a softening agent than can usually be afforded in the operating room and, furthermore, if one has to resort to alcohol one might just as well use nonboilable gut which is already put up in alcohol and is sufficiently pliable for immediate use when removed from the tube. An additional point regarding the use of alcohol as a softening agent and as a solvent for the xylene revolves about an observation in Exper. 3, where it was found that in certain concentrations of xylene in 95% alcohol there was apparently a greater tissue reaction observed than when either xylene or alcohol was used alone.

It is probable that some of the recently developed "wetting agents" or emulsifiers might be useful in removing the xylene from the gut. A relatively small amount of one of these in water will emulsify the xylene and favor its removal from the gut. Studies are in progress to determine what agents of

this type might be best suited to the elimination of water-insoluble irritants from surgical gut

Although our data show that toluene is definitely less irritant and necrosing to tissues than xylene it is more of an irritant than is desirable. Furthermore, the use of toluene as a tubing fluid would subject the operating team to the hazards of inhaling toluene vapor. There has been considerable interest recently in the hazards of inhaling toluene vapor in concentrations of 50 to 200 ppm* (von Oettingen, and co-workers,^{5, 6} and Greenburg, and co-workers⁷). It is not inconceivable that in a busy and not too well ventilated operating room the operating team could be exposed to a concentration of toluene vapor from the broken tubes of surgical gut sufficient to produce some of the toxic manifestations, muscle incoordination in particular, described by von Oettingen. Xylene appears to have very similar toxic properties.⁸

If manufacturers are unable to provide an anhydrous liquid for boilable surgical gut which is not only harmless to the gut, but also harmless to tissues and nontoxic when inhaled as a vapor it would appear appropriate to suggest marketing boilable products without any tubing fluid. For surgeons who are anxious to utilize suture material which is entirely free of extraneous irritants this would provide the ideal absorbable suture. It would be necessary, of course, to moisten the gut in physiologic salt solution to make it pliable.

NONBOILABLE TUBING FLUID—The data from Experi 4 and 5 show that there was a water-insoluble liquid present in varying concentrations, up to 15% by volume, in the alcoholic tubing fluid of numerous nonboilable surgical products. Neither the presence of such a liquid nor its nature was indicated on the package label where the composition of the tubing fluid is supposed to be recorded. With the cooperation of an independent laboratory this observation was further substantiated, and the water insoluble liquid identified as a high boiling range hydrocarbon mixture.

The explanation for the presence of this high boiling range water-insoluble liquid in the alcoholic tubing fluid is undoubtedly that it represents the material in which the surgical gut was heat sterilized, and this anhydrous liquid was not completely removed from the tube containing the gut before the alcoholic solution was added and the tube sealed. The striking differences in the amount of such material present in the alcoholic tubing fluids from different commercial sources (Table II) make it appear obvious that there are fundamental differences in the way various companies handle this step in the manufacture of surgical gut. Furthermore, variations were occasionally observed in this respect from tube to tube and from lot to lot in products from the same manufacturer. It is apparent from these observations that this step in the production of nonboilable surgical gut deserves considerably more attention from the manufacturers than it has received up to the present time. It is only

* Parts per million

fair to point out here that some manufacturers have been eliminating this material from their finished products to a considerable degree. It was rather surprising to find, on the other hand, that in some products as much as 5 to 15 per cent of the alcoholic tubing fluid was in all probability the liquid which had been used in the heat sterilization process.

The presence of this material in alcoholic tubing fluids would have little practical significance were it not for its striking properties as a tissue irritant. In Exper 8 it was shown that all the nonboilable tubing fluids were more irritant to human tissues than 95% ethyl alcohol. Furthermore the degree of tissue reaction induced by these fluids was roughly proportional to the concentration of the water-insoluble component. It was of some interest that even traces of this material in the tubing fluid appeared to cause a more noticeable reaction than 95% alcohol. It is possible that the tissue reaction produced by products having only a trace of water-insoluble component may have been due to irritant substances extracted from the suture material by the alcohol, or to some denaturant which may have been present in the commercial grade of alcohol employed. These explanations are probably of minor significance, however, in view of the obvious necrosing action in human skin of concentrations as low as 1% in 95% ethyl alcohol (C P) of the pooled high boiling range distillate from alcoholic tubing fluids (Fig 7).

The use of a petroleum derivative by at least one manufacturer, presumably to avoid using the irritant coal-tar derivatives, did not eliminate the irritant factor in the alcoholic tubing fluid because this material or at least the sample available to us was no less irritating and necrosing to tissues than hi-flash solvent.

In regard to the use of an alcoholic solution for the tubing fluid of non-boilable surgical gut it should be pointed out that 95 per cent ethyl alcohol is a tissue irritant and protein coagulant. Its irritant action in the tissues is, however, substantially less than xylene hi-flash solvent, the petroleum derivative, and even less than toluene. Its mode of action is somewhat different as pointed out in Exper 3 and 8. It is probable that such irritant action as may be observed in the tissues from catgut is only secondarily due to alcohol in view of the potent irritant action of the water-insoluble hydrocarbons which undoubtedly overshadows the action of the alcohol or is enhanced by it. In most operating rooms there is some lapse of time between the opening of the tube and the use of the catgut and it is hoped that some of the alcohol has an opportunity to evaporate before the gut is introduced into the tissues. If the alcoholic tubing fluid is relatively free from water-insoluble hydrocarbon, and if the catgut is stretched out and permitted to dry or is moistened in saline, it is probable that this would represent the suture material of least extraneous irritant content which is now available.

The presence of germicidals such as potassium mercuric iodide and phenyl mercuric benzoate in the alcoholic tubing fluids offers another source of irritation, but our limited observations on this point lead us to believe it is rela-

tively insignificant in comparison with the potent irritant action of the hydrocarbon factor of tubing fluids

The presence of appreciable quantities of a water-insoluble liquid in alcoholic tubing fluids, which was demonstrated to have an irritant action in relatively low dilutions in alcohol, and which evaporates more slowly than alcohol, could account for considerable tissue irritation if introduced into the tissues along with surgical gut sutures

The demonstration of a water insoluble liquid in alcoholic tubing fluid by the emulsion tests or other means does not necessarily imply that such a liquid is an irritant to tissues because some manufacturers may find a suitable anhydrous liquid for heat sterilization which is harmless to living tissues. Therefore, any residuum of such liquid in alcoholic tubing fluids would not constitute a potential source of tissue irritation if carried into the tissues along with the surgical gut

In regard to the identity of the fluid which was found in the alcoholic tubing fluids this may be said. It has a characteristic odor, a boiling range, a solubility in water-alcohol mixtures, and a tissue irritant action which was closely similar to that observed for a hydrocarbon known as hi-flash solvent, which is believed to be the anhydrous liquid used by most manufacturers for the heat sterilization of their catgut

SUMMARY

1 Xylene, which has been the anhydrous liquid commonly used as a tubing fluid for boilable surgical gut, was found to be a potent tissue irritant

2 The alcoholic tubing fluids of nonboilable surgical gut were found to contain, in many instances, a water-insoluble liquid the presence of which could be demonstrated by the addition of water which produced a white emulsion

3 The amount of this water-insoluble liquid varied in different products package lots, and individual tubes in the same package from a trace to as much as 15 per cent by volume of the alcoholic tubing fluid

4 The irritant action of the alcoholic tubing fluids were generally in excess of that observed for 95 per cent ethyl alcohol, but less than was found for xylene. The magnitude of irritant action, which in some products was rather excessive, was proportional to the amount of water-insoluble liquid in the alcoholic tubing fluid

5 The water-insoluble liquid recovered from the alcoholic tubing fluids by emulsion separation or distillation was found to be somewhat more of a tissue irritant than xylene

CONCLUSIONS

1 The presence of a water-insoluble liquid in alcoholic tubing fluid of non-boilable surgical gut can probably be explained on the basis that it represents a residuum of the anhydrous hydrocarbon used for the heat sterilization of the catgut, which was not eliminated from the tube before the addition of the alcoholic solution and the sealing of the tube

2 In view of the irritant action of xylene and this water-insoluble liquid in alcoholic tubing fluids, which was probably hi-flash solvent or a similar or related anhydrous hydrocarbon, a question is raised as to whether these liquids alone or in combination with alcohol may not be carried into the tissues along with surgical gut in sufficient concentration to have an undesirable irritant action on the tissues in which the catgut is placed

3 The use of an anhydrous liquid in the heat sterilization of catgut to obtain uniform transmission of heat without damage to the gut is conceded as a necessary step in the manufacture of surgical gut to insure the standard of sterility expected by the surgical profession. However, it would appear that general improvements could be made in some manufacturing methods from the standpoint of utilizing a liquid for heat sterilization which is nonirritating to tissues or of eliminating from tubing fluids such hydrocarbons as have been found to have irritant properties to living tissues

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HYDROCARBON CONTENT OF NONBOILABLE SURGICAL GUT TUBING FLUIDS^{*}

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CURRENTLY MARKETED nonboilable surgical gut is packaged in sealed glass tubes, scored for breaking at the midpoint. Each tube contains a single strand of surgical gut with or without a spool, a loose paper label insert, and a quantity of clear fluid known as "tubing fluid." According to requirements of the United States Pharmacopeia, the composition of the tubing fluid used in packaging surgical gut must be stated in the labeling of market packages of the product.

In the course of a study of tissue irritation associated with the tubing fluids employed in marketing surgical gut, Drs. H. P. Jenkins and C. L. Dunham, of the University of Chicago, observed that the admixture of water with the tubing fluids from some brands of nonboilable surgical gut produced white emulsions of varying turbidity. These investigators found that the emulsions thus formed broke on standing, with the formation of water-immiscible, supernatant liquid layers of varying volume. These findings were brought to the attention of the A. M. A. Chemical Laboratory. Because of the possible serious implications, an independent chemical examination was made of the tubing fluids used in packaging nonboilable surgical gut marketed by various manufacturers. For this purpose, original market packages of size one, nonboilable, sterile surgical gut of both plain and medium chromic types, representative of the products of nine different manufacturers, were purchased on the open market for examination.

According to statements found on the package labels, the tubing fluids used in the products obtained may be classified as follows:

- (a) 95 per cent ethyl alcohol containing varying amounts (0.1 to 0.3 per cent) of potassium mercuric iodide
- (b) 76 per cent ethyl alcohol, 20 per cent isopropyl alcohol and phenylmercuric benzoate 0.025 per cent in water
- (c) 95 per cent ethyl alcohol containing phenylmercuric benzoate 0.02 per cent
- (d) Anhydrous ethyl alcohol containing 10 per cent methanol
- (e) 97 per cent ethyl alcohol containing phenylmercuric nitrate 0.025 per cent

It is apparent that this classification includes no water-insoluble liquid constituents. However, the results of this investigation indicate the presence of up to 14 per cent (V/V) of water-insoluble liquid aromatic hydrocarbons in some of the nonboilable surgical gut "tubing fluids" examined. The physical and chemical properties of the water-insoluble materials isolated from various specimens lead to the conclusion that the tubing fluid contains mate-

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rial closely related to a coal-tar distillate, the so-called "xylene fraction" or solvent naphtha. Specimens of the hydrocarbons isolated from nonboilable tubing fluids in this laboratory were submitted to Doctors Jenkins and Dunham.¹ Injection of these materials, when administered either undiluted or in the form of alcoholic solutions, produced tissue irritation.

TABLE I
AROMATIC HYDROCARBON CONTENT OF SURGICAL GUT TUBING FLUID

Manufacturer*	Gut Type	Odor Test	Per Cent Hydrocarbon Found (V/V)	Principal Boiling Range of Isolated Hydrocarbons
1	A	—	2.5\	167°-170° C
	C	+	4.8f	
2	A	+	1.9\	172°-174° C
	C	+	0.7f	
3	A	—	0.4	
	C	—	0.03	
4	A	+	3.3\	152°-174° C
	C	+	2.6f	
5	A	—	0.02\	154°-158° C
	C	+	5.9f	
6	A	—	0.15	
	C	—	0.10	
7	A	—	0.05	
	C	—	0.05	
8	A	+	14.0\	152°-174° C
	C	+	6.8f	
9	A	+	1.4	
	C	+	0.6	

*The method of indicating manufacturer by the numbers 1, 2, 3, etc., does not represent the same code as that used by Jenkins and Dunham.

EXPERIMENTAL STUDIES

Original market packages of size one, nonboilable surgical gut (U.S.P.), of both Type A (plain) and Type C (medium chronic) were purchased from a surgical supply house. The products of nine different manufacturers were obtained. The fluids found in individual tubes served as specimens for study.

A. Odor. The odor of the tubing fluid contained in individual tubes was used as a rough index of the presence or absence of aromatic hydrocarbons. It was found that tubing fluids, later shown to contain less than 0.4 per cent (V/V) of aromatic hydrocarbons yielded only the odor of the alcohols present. Positive results obtained by the odor test are shown in Table I by plus (+) signs.

B. Composite Distillate. Tubing fluids whose odors indicated the presence of aromatic hydrocarbons were pooled and mixed with ten volumes of water. Sufficient normal sodium hydroxide to render the emulsion alkaline was added and the mixture was distilled. The initial portion of the distillate was cloudy emulsion. The distillation was continued until only a single fluid was discharged from the condenser. The collected distillate was treated with two volumes of water, acidified with diluted sulfuric acid, and distilled again, until only a single fluid was discharged from the condenser. The final distillate was treated with two volumes of water and allowed to stand in a stoppered

graduated cylinder until the white emulsion broke and a clear supernatant liquid layer formed. The liquids were separated and the water-insoluble material was dried with anhydrous sodium sulfate. On distillation, the boiling point range of this material was found to be from 140° to 190° C. The total distillate was divided into two portions. One portion was submitted to Doctors Jenkins and Dunham for tissue irritation studies, the other was retained for chemical examination. The isolated fluid burned in air with a yellow, smoky flame. One volume of the liquid was found to be soluble in three volumes of fuming sulfuric acid. Qualitative tests indicated the absence of halogens, nitrogen and sulfur. The refractive index of the liquid was found to be 1.49 at 25° C, and the specific gravity found was 0.861 at 25° C. It was soluble in ethyl alcohol, methyl alcohol and isopropyl alcohol, but insoluble in water. Traces of the material yielded a reddish-brown color with concentrated sulfuric acid containing small amounts of formaldehyde.

C Individual Tubing Fluids Material isolated, as described in (B), was used as a control substance, dissolved in alcohol, in the further investigation of individual tubing fluids. An adaptation of the British² standardized test for benzene in air was applied to individual tubing fluids in appropriate ethyl alcohol dilution. The prepared solutions were transferred to an apparatus designed to allow aspiration of a measured volume of air through the unknown solution and thence through a known volume of a reagent consisting of five cubic centimeters of 40 per cent formaldehyde solution per 100 cc of concentrated sulfuric acid. Spectrophotometric measurements at 500, 550 and 600 m on the colored solutions obtained indicated the presence of up to 14.0 per cent (V/V) of aromatic hydrocarbons in the various original tubing fluids studied. The results are shown in Table I.

D Hydrocarbons from Individual Tubing Fluids Specimens of tubing fluid from individual products found by test to contain aromatic hydrocarbons were distilled from aqueous solutions as described under (B), and portions of the hydrocarbons obtained were submitted to Doctors Jenkins and Dunham for tissue irritation studies. The isolated materials were found to be completely soluble in fuming sulfuric acid and responded to tests for aromatic hydrocarbons. The boiling points found are shown in Table I.

SUMMARY

Chemical examination of marketed specimens of nonboilable surgical gut (U S P), representing products of nine different manufacturers, indicated the presence of up to 14.0 per cent (V/V) of high boiling aromatic hydrocarbons in the tubing fluids. These hydrocarbons are related to a coal-tar distillate known as the "xylene fraction" or solvent naphtha.

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IRRITANT PROPERTIES OF TUBING FLUIDS AS A FACTOR IN THE TISSUE REACTIONS OBSERVED WITH SURGICAL GUT (CATGUT)¹

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In the previously reported work on the "Absorption of Surgical Gut (Catgut¹)" it was pointed out in the discussion of the possible explanations of the tissue irritation which frequently was associated with the experimental catgut implants that this may have been due to irritants in the tubing fluid such as the xylene of boilable products, the alcohol of nonboilable products, or the water-insoluble liquid which was found to be present in some non-boilable alcoholic tubing fluids. The surgical gut tubing fluids were made the subject of further study to clarify this point, and preliminary reports of this work have already appeared.²

In the preceding communication by Dunham and Jenkins³ it was found that the surgical gut tubing fluids were tissue irritants of varying degree depending on the composition of the fluid. The irritant properties were evaluated by the intradermal injection of 0.05 cc amounts of the various fluids into the skin of dogs and human subjects and observing the lesions produced thereby. The boilable variety of surgical gut tubing fluid, which was xylene, was found to be especially damaging to tissues. The nonboilable variety of tubing fluids which were recorded on the package label as consisting of various alcoholic solutions containing a fraction of one per cent of a germicidal agent, was somewhat less damaging to tissues than the xylene tubing fluid, however, the magnitude of the tissue reaction was frequently considerably in excess of that obtained by 95 per cent ethyl alcohol. This excessive irritant action of a considerable proportion of the alcoholic tubing fluids as compared with 95 per cent ethyl alcohol was apparently due to the presence of a water-insoluble liquid in the alcoholic tubing fluids. The amount of this liquid varied from a trace to as much as 15 per cent by volume in the various products tested. The presence of this water-insoluble liquid in the nonboilable surgical gut tubing fluids was further corroborated by Sidwell,⁴ and identified as a high boiling range aromatic hydrocarbon mixture related to a coal-tar distillate known as "xylene fraction" or solvent naphtha.

The presence of this water-insoluble liquid in the alcoholic tubing fluids of nonboilable surgical gut undoubtedly represented a residue of the anhydrous liquid which was used by the manufacturer for the heat sterilization of the catgut and which was not eliminated from the tube of catgut before the

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alcoholic solution was added and the tube sealed. This liquid was found to be somewhat more damaging to tissues than xylene and its irritant action could be detected in relatively low dilutions in 95 per cent ethyl alcohol. A sample of the liquid which was believed to be the anhydrous hydrocarbon used by most of the surgical gut manufacturers, and which has been known as hi-flash solvent, was found from the standpoint of tissue irritation, solubility in water-alcohol mixtures, and boiling range to have properties similar to the water-insoluble liquid which was recovered from most of the alcoholic tubing fluids.

The practical significance of these observations on the irritant properties of surgical gut tubing fluids depends upon whether the tubing fluids are carried into the tissues along with the catgut in sufficient concentration to have an irritant action on the tissues in which the catgut is embedded.

In an endeavor to evaluate this point a number of experiments were devised. 1. Weighings were made of catgut to determine the amount of tubing fluid which remained on or in the catgut strand after removal from the tube. 2. Intradermal injection tests were carried out on dogs and patients utilizing amounts and concentrations of xylene or hi-flash solvent which were comparable to that found in the catgut by the weighing experiments. 3. Implantations of catgut in the tissues were made with and without washing procedures designed to eliminate tubing fluid irritants.

EXPERIMENTAL STUDIES

1. **WEIGHING TESTS**—*Boilable Catgut*. Standard tubes of boilable catgut, which contained xylene as the tubing fluid according to the package label, were opened, the catgut was wiped with a dry cloth and then weighed, utilizing a glass-encased high sensitivity scale (sensitive to 0.1 mg). The catgut was then placed in a vacuum desiccator and removed for subsequent weighings until such time as a constant weight was obtained.

	Weight	Loss of Weight	Concentration of Volatile Material
NO. 2 SIZE OF TYPE A—PLAIN SURGICAL CUT			
Original	0.3612 Gm		
40 minutes	0.3585 Gm	2.7 mg	
3 hours	0.3565 Gm	4.7 mg	
20 hours	0.3561 Gm	5.1 mg	1.4%
NO. 2 SIZE OF TYPE A—PLAIN SURGICAL GUT			
Original	3.975 Gm		
35 minutes	3.944 Gm	3.1 mg	
3 hours	3.925 Gm	5.0 mg	
20 hours	3.925 Gm	5.0 mg	
7 days	3.924 Gm	5.1 mg	1.28%
NO. 2 SIZE OF TYPE C—MEDIUM CHROMIC SURGICAL GUT			
Original	0.3128 Gm		
35 minutes	0.3117 Gm	1.1 mg	
3 hours	0.3074 Gm	5.4 mg	
20 hours	0.3070 Gm	5.8 mg	
5 days	0.3052 Gm	7.6 mg	2%
NO. 1 SIZE OF TYPE A—PLAIN SURGICAL GUT			
Original	0.3970 Gm		
45 minutes	0.3924 Gm	4.6 mg	
3 hours	0.3912 Gm	5.8 mg	
24 hours	0.3898 Gm	7.2 mg	
48 hours	0.3893 Gm	7.7 mg	1.9%

To determine the adequacy of the wiping procedure to eliminate the xylene on the surface of the gut additional tests were carried out in which the surface xylene was eliminated by subjecting the gut to a preliminary ten-minute period of vacuum desiccation as soon as it was removed from the tube. This period of time was apparently adequate for the elimination of the xylene on the surface of the gut.

NO. 2 SIZE OF TYPE C—MEDIUM CHROMIC SURGICAL CUT

Original	Weight	Loss of Weight	Concentration of Volatile Material
10 minutes	0.3556 Gm		
	0.3442 Gm	11.4 mg.	3.2%
1½ hours	0.3427 Gm	1.5 mg	
20 hours	0.3390 Gm	5.2 mg	1.5%
3 days	0.3374 Gm	6.8 mg	1.9%

It would appear from these observations that practically all of the surface xylene was eliminated from the gut by the initial vacuum treatment, in view of the fact that in the next hour and one-half only 1.5 mg. were eliminated. It should be of particular interest that the most substantial portion of the residual xylene was not recovered until the following day. The residual concentration of volatile material of 1.9 per cent after elimination of surface xylene compares favorably with the results obtained by wiping the gut before obtaining the original weight.

These observations establish the fact that one to two per cent by weight of the larger sizes of boilable catgut consists of volatile material which appears to be within the strand of gut rather than on its surface. The relatively long periods of time required to eliminate this volatile material from the gut by vacuum desiccation is a point of considerable importance. Boilable gut must be prepared in a strictly anhydrous condition and if this amount of weight loss were due to water in the gut it is very probable that the heat sterilization process would have seriously damaged the gut which is quite vulnerable to heat in the presence of any appreciable amount of moisture. Therefore, the one to two per cent loss of weight which was found after elimination of surface xylene was presumed to represent the concentration of xylene within the strand of catgut and which was eliminated only by prolonged treatment in the vacuum desiccator. It is very improbable that this would be eliminated by the operating room procedures customarily utilized for inducing pliability of the gut before its use in the tissues such as dipping in water, saline or 70 per cent alcohol for a few minutes.

Nonboilable Catgut. Standard tubes of nonboilable surgical gut which contained alcoholic tubing fluid and a germicidal agent, according to the package label, were opened, the frame supporting the gut was removed, and the strand weighed immediately. Then the strand was stretched out as is customarily done in the operating room as soon as it is removed from the tube and weighed again.

Following this, the strand was placed in the vacuum desiccator and re-

SURGICAL CATGUT TUBING FLUID

moved from time to time for subsequent weighings. The original weight used for computing the ultimate loss of weight was the reading taken after stretching out the catgut, as this is more nearly representative of the condition of the gut when it is used in the operating room.

NO. 2 TYPE A—PLAIN SURGICAL GUT (5% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

	Weight	Loss of Weight	Significant Concentration of Volatile Material (Alcoholic Tubing Fluid)
Original	0.6240 Gm		
After stretching	0.5820 Gm	42.0 mg	
1 hour	0.5204 Gm	61.6 mg	
20 hours	0.4840 Gm	98.0 mg	16.8%
3 days	0.4728 Gm	109.2 mg	18.7%

NO. 2 TYPE C—MEDIUM CHRONIC SURGICAL GUT (2% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

Original	0.5704 Gm		
After stretching	0.5348 Gm	35.6 mg	
1 hour	0.4717 Gm	63.1 mg	
20 hours	0.4403 Gm	94.5 mg	17.6%
3 days	0.4302 Gm	104.6 mg	19.3%

NO. 1 TYPE A—PLAIN SURGICAL GUT (5½% HYDROCARBON IN ALCOHOLIC TUBING FLUID)

Original	0.5050 Gm		
After stretching	0.4830 Gm	22.0 mg	
1 hour	0.4297 Gm	55.3 mg	
20 hours	0.4000 Gm	83.0 mg	17%
3 days	0.3907 Gm	92.3 mg	19.3%

NO. 1 TYPE C—MEDIUM CHRONIC SURGICAL GUT

Original	0.3600 Gm		
After stretching	0.3520 Gm	8.0 mg	
1 hour	0.3128 Gm	39.2 mg	
20 hours	0.2946 Gm	57.4 mg	16.2%
3 days	0.2887 Gm	63.3 mg	17.9%

These observations establish the fact that as much as 18 per cent by weight of the larger sizes of nonboilable surgical gut may be composed of volatile material when it is used in the operating room as soon as it is removed from the tube and stretched out according to directions of the manufacturer. If the catgut is not stretched out before it is used it may have as much as 22 per cent by weight of volatile material in or on the catgut. The volatile component of the surgical gut is presumably the alcoholic tubing fluid which, in this instance, was recorded on the package label as 96 per cent alcohol but which also was found to contain appreciable quantities of a water-insoluble liquid which is believed to be hi-flash solvent. Thus, we have three components to consider, the alcohol, the water and the hi-flash solvent (B.P.) 163°-180° C. In view of the rather striking differences in the boiling points of these three liquids it would not be surprising to find some selectivity in their elimination from the gut in the vacuum desiccator. The presence of 18 per cent alcohol by weight, of course, would mean a considerably higher concentration if estimated from the standpoint of volume in view of the low specific gravity of alcohol. Thus, we have to consider that at least 20 per cent by volume of the catgut is volatile material. With this point estab-

lished we must also take into consideration that there may be from five per cent to ten per cent of hi-flash solvent in some of the alcoholic tubing fluids. Surgical gut which is put up in such a tubing fluid would then be expected to have at least a concentration of one to two per cent by volume, or 0.9 per cent to 1.8 per cent by weight of hi-flash solvent in the gut.

Aside from the relative concentration of xylene or hi-flash solvent, which may be as much as one to two per cent in the catgut, one should take into consideration the actual amount present in the length of catgut which is required for a single ligature. It requires approximately 3 cm. of a No. 1-size catgut for an ordinary ligature if a triple throw knot is used and the ends of the strand cut within two to three millimeters of the knot. There are approximately 150 cm. of catgut in a standard strand. Therefore, if one has as much as five milligrams or more, of xylene present in the entire strand one would have at least 0.1 mg. in three centimeters of catgut concentrated in a relatively small focal point. Similar analogies obtain in regard to hi-flash solvent if it is present in five to ten per cent concentrations in the alcoholic tubing fluid. Subsequent intradermal injection experiments will demonstrate the effect of this amount of material in the tissues. In regard to the alcohol in the non-boilable catgut there may be as much as 1.5 mg. of alcohol in a single ligature of No. 1 catgut, aside from any hi-flash solvent component.

These tests demonstrate that it requires an hour of vacuum dessication to eliminate 60 per cent of the volatile material in nonboilable surgical gut which would appear to be alcohol, water and a trace to as much as 15 per cent of a high boiling point hydrocarbon. Therefore it is improbable that more than half of the tubing fluid would be eliminated by evaporation during the course of an ordinary operation if the gut was removed from the tubes at the beginning of the operation. Furthermore, it is likely that the material with the high boiling range would remain in the gut longer than the alcohol. Whatever tubing fluid that fails to be eliminated by evaporation would obviously be carried into the tissues along with the suture.

2. INTRADERMAL INJECTION EXPERIMENTS—To ascertain the action on the tissues of relatively minute amounts of the water-insoluble hydrocarbons xylene and hi-flash solvent, they were made up in varying concentrations as an emulsion in physiologic saline solution, with the aid of an emulsifying agent such as Nimol 737 or Atlas Tween 20. Intradermal injections of 0.05 cc. amounts were made in the skin of dogs and patients and the resulting lesions observed.

In the series of injection experiments on animals, 10 per cent, 5 per cent, 1 per cent, and 0.5 per cent emulsions of xylene and hi-flash solvent in saline were used. The concentration of emulsifying agent (Nimol 737) in the 10 per cent emulsion was 2 per cent; in the 1 per cent emulsion 0.2 per cent. In addition, 10 per cent, 5 per cent and 1 per cent dilutions of concentrated HNO_3 were used for comparison. The results of these tests showed that the 10 per cent and 5 per cent emulsions of xylene or hi-flash solvent were capable of producing necrosis of the skin whereas the 1 per cent and 0.5 per cent

emulsions produced small inflammatory lesions which subsided after several days without producing necrosis. The emulsifying agent alone in the 2 per cent concentration produced a small nonnecrotizing inflammatory lesion, but in 0.5 per cent to 0.2 per cent concentrations the lesion produced was practically negligible. The 10 per cent and 5 per cent nitric acid solution produced skin necrosis which was somewhat less conspicuous than was observed for the 10 per cent and 5 per cent emulsions, but in the 1 per cent HNO₃ concentration the lesion was somewhat more noticeable than the 1 per cent emulsion preparations but did not go on to necrosis.

In another series of animals 5 cc of Evans blue (T-1824) was injected intravenously before the intradermal injections were made. It was of considerable interest to observe that emulsion preparations as well as the dilutions of HNO₃ produced a blue discoloration of the skin at the site of injection which was noticeable within a few minutes and spread to an area of 1-2 cm about the site of injection. This would appear to indicate that a fairly rapid damaging effect of the capillaries is obtained with loss of plasma at the point of injection. Some blue discoloration occurred for the 2 per cent Nimol as well as for distilled water which was also used in this series as a control. The distilled water injection produced a temporary lesion which did not go on to necrosis. No noticeable blue color was found at the site of injection of the saline controls or the 0.5 per cent or 0.2 per cent emulsifying agent (Nimol).

In the intradermal skin tests on patients 1 per cent, 0.5 per cent, 0.1 per cent and 0.05 per cent emulsions of xylene or hi-flash solvent in physiological saline were used in 0.05 cc or 0.025 cc amounts. Nimol in 0.2 per cent concentration was used for some of the 1 per cent emulsions, whereas Atlas Tween 20 was used in most of the tests in 0.5 per cent concentration in the 1 per cent emulsions. The more dilute emulsions contained proportionately less emulsifying agent, that is the 0.1 per cent emulsion contained only 0.05 per cent of emulsifying agent. Sixteen patients were subjected to injection tests, the results of which showed that the 1 per cent emulsions of xylene or hi-flash solvent rather consistently produced a small inflammatory lesion at least 1 cm in diameter which could be detected up to one to three weeks after injection as a small area of induration or redness. The injection produced considerable pain. The 0.5 per cent emulsions produced similar but slightly less conspicuous lesions. The 0.1 per cent emulsions produced a noticeable inflammatory lesion which generally lasted for one to three days or sometimes longer, although in some instances these were difficult to detect after 24 hours. The 0.05 per cent emulsion injections produced relatively transient lesions which were difficult to identify after 24 hours although in one patient the lesion could be detected for two days after the injection. The controls of 0.5 per cent Tween 20 in saline produced transient lesions which were relatively minimal in comparison with the 1 per cent emulsions with which they were compared. The saline controls did not produce any persistent detectable lesions. Distilled water controls produced a transient lesion

which was painful at the time of injection. There was a slight pain sensation associated with the 0.5 per cent Tween 20 controls, and slightly more pain with the 0.1 per cent emulsions. There was no noticeable difference in the effect of the xylene as compared with hi-flash solvent in comparable dilutions in the same patient.

To compare the weighing experiments mentioned above with the amount of xylene or hi-flash solvent used in the intradermal tests the following table is presented which gives the amount of hydrocarbon in cubic centimeters and milligrams which is present in the 0.05 cc. of emulsion which was used for injection purposes.

1%	0.5%	0.1%	0.05%
0.0005 cc	0.00025 cc	0.00005 cc	0.000025 cc
5/10,000 cc	25/100,000 cc	5/100,000 cc	25/1,000,000 cc
0.13 mg	0.215 mg	0.043 mg	0.0215 mg

In the weighing experiments it was found that 3 cm. of No. 1 catgut could contain as much as 0.1 mg. of xylene or a similar amount of hi-flash solvent if the concentration of this was 5 per cent or more in the alcoholic tubing fluid which was not at all uncommon in many nonboilable products. Therefore, the amount of irritant hydrocarbon which may be present in a single ligature of No. 1 catgut is approximately midway between the hydrocarbon content of the 0.5 per cent and the 0.1 per cent emulsion injections. In view of the fact that these concentrations of hydrocarbon will produce evidence of inflammatory reaction in the tissues of patients which were subjected to test it is reasonable to presume that the hydrocarbon content of a single ligature is capable of producing an inflammatory reaction about the catgut.

In four patients it was possible to obtain a microscopic section of the lesions produced by the injection tests. The tissue was obtained by operation, such as amputation or excision of a tumor or scar requiring removal of adjacent normal skin, or by punch biopsy. In three of these sections which were made through lesions produced by 1 per cent or 0.5 per cent emulsions of hi-flash solvent there was a definite polymorphonuclear leukocytic invasion of the tissues which was limited to the area of injection. In the punch biopsy of the lesion produced by 0.1 per cent emulsion the leukocytic invasion was less marked (Fig. 1).

3. SURGICAL IMPLANTS IN THE TISSUES. A series of dogs were subjected to implantation tests using as many as six different standard products. Some of the implantations were done with boilable gut and others with nonboilable gut. The animals were operated upon under ether anesthesia, and the implantations made in the abdominal muscles under aseptic technic, as described in the previously reported work on "Absorption of Surgical Gut." The boilable variety of catgut was implanted direct from the tube, after dipping in 70 per cent alcohol or saline long enough to induce pliability, after prolonged washing in 95 per cent alcohol, and after subsequent washing in saline. Non-

boilable products were implanted after removal from the tubes, and after prolonged washing in alcohol

The results of these tests showed that in boilable products there was tissue irritation about the catgut implant which was manifest grossly as exudate and microscopically as an intense polymorphonuclear leukocytic invasion of the surrounding tissues, unless rather prolonged washing in 95 per cent ethyl alcohol had been previously carried out and the catgut dried or subsequently washed in saline. Even this procedure did not eliminate evidence of irrita-

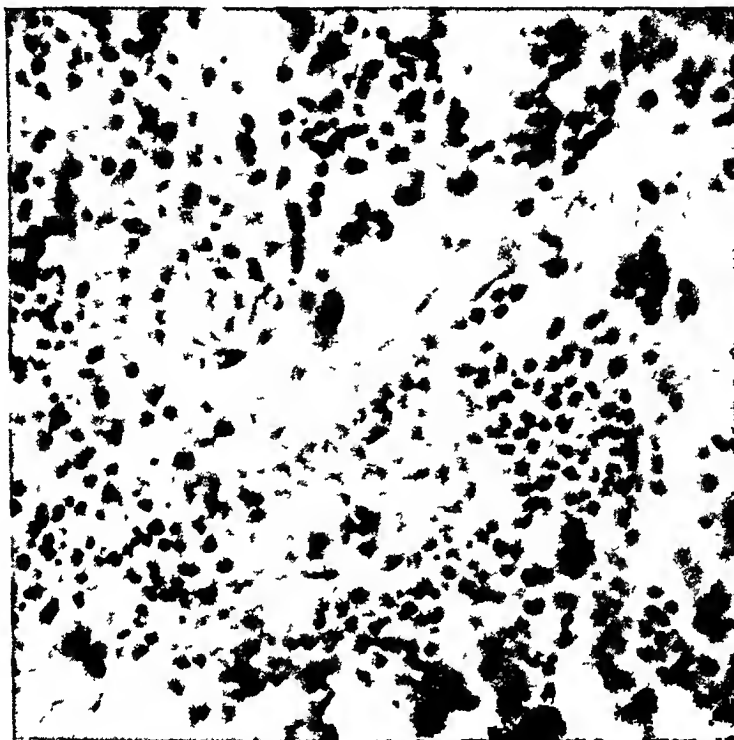


Fig 1—Showing cellular response 24 hours after the injection of a 0.5% emulsion of tubing fluid hydrocarbon in patient. This represents 0.215 mg of hydrocarbon. The rather striking polymorphonuclear leukocytic invasion of the tissues at the site of injection is an index to the irritant property of such liquids. At least this amount of hydrocarbon may be present in the length of gut required for two ligatures of No. 1 size of catgut if the original tubing fluid were xylene or an alcoholic solution containing 5% or more of a similar hydrocarbon, and prepared for surgical use by ordinary operating room technics.

tion in many instances, although it did tend to minimize it. Dipping the catgut in water or 70 per cent alcohol for a period of time which is adequate to induce pliability such as is the custom in operating rooms where boilable products are used did not appear to eliminate to any appreciable extent the evidence of tissue irritation (Fig 2).

Another point which deserves mention is that in a number of instances where boilable products were implanted on one side of the abdominal wall of dogs and nonboilable products which were relatively free from hydrocarbons on the opposite side, it was found that a rather striking difference could be observed on the two sides from the standpoint of extensive edema of the abdominal wall where the boilable products had been implanted. Xylene is capable of producing edema of this magnitude in the tissues.

In the nonboilable products the washing in 95 per cent ethyl alcohol for a day or more and subsequent drying usually resulted in the elimination of gross evidence of tissue reaction such as exudate, however, there was microscopic evidence of polymorphonuclear invasion about certain products which

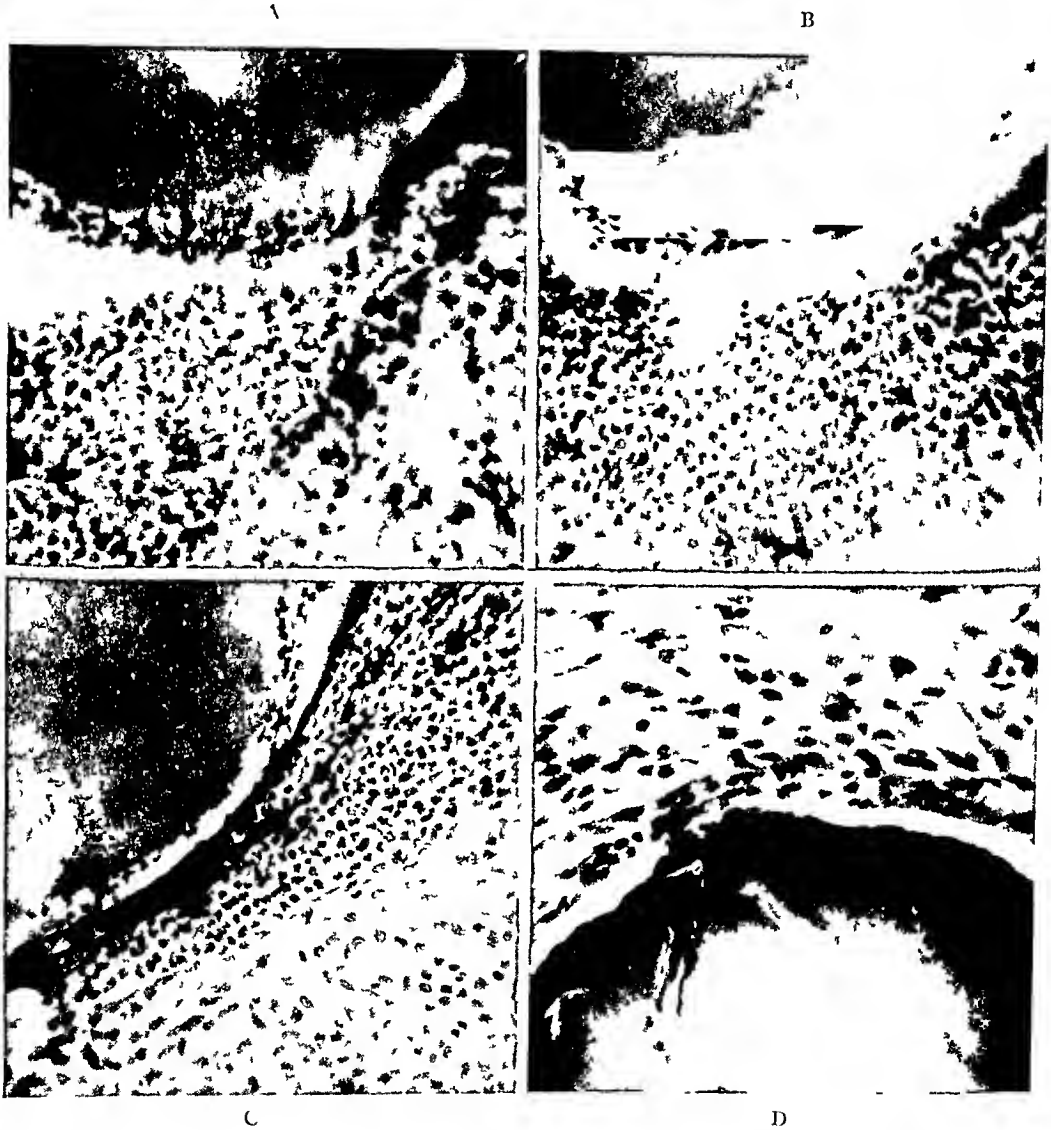


FIG 2—Showing tissue response to portions of the same strand of No. 000 size of Type C medium chromic boilable surgical gut after ten days in the tissues of the same animal. A Implanted direct from xylene tubing fluid and showing excessive polymorphonuclear leukocytic invasion of the tissues about the gut. B Implanted after dipping in 70% alcohol long enough to induce pliability and showing conspicuous leukocytic response. C Implanted after dipping in water long enough to induce pliability and showing leukocytic response. D Implanted after washing in 95% ethyl alcohol for 24 hours and subsequent washing in saline for six hours, and showing practically no leukocytic response, only fibroblasts and macrophages. This represents as minimal amount of tissue reaction as could be obtained with any type of suture material.

were generally those which had the most hydrocarbon in the original alcoholic tubing fluid. The catgut which gave the least evidence of irritation as evidenced by minimal leukocytic response was usually that which was relatively free from hydrocarbon in the alcoholic tubing fluid (Fig 3). In comparing these observations with previous implants, which were done in the course of

the work on the Absorption of Surgical Gut, it was quite obvious that the excessive exudate which characterized certain products was substantially reduced by washing in 95 per cent ethyl alcohol as compared with what was usually previously observed. Furthermore, it was observed that unless the alcoholic solution was permitted to evaporate to some extent before implanting the catgut one may have evidence of appreciable irritation in the tissues without the presence of any hydrocarbon in the alcoholic solution. This is not surprising in view of the known irritant action of alcohol, which was further demonstrated in previous injection experiments.

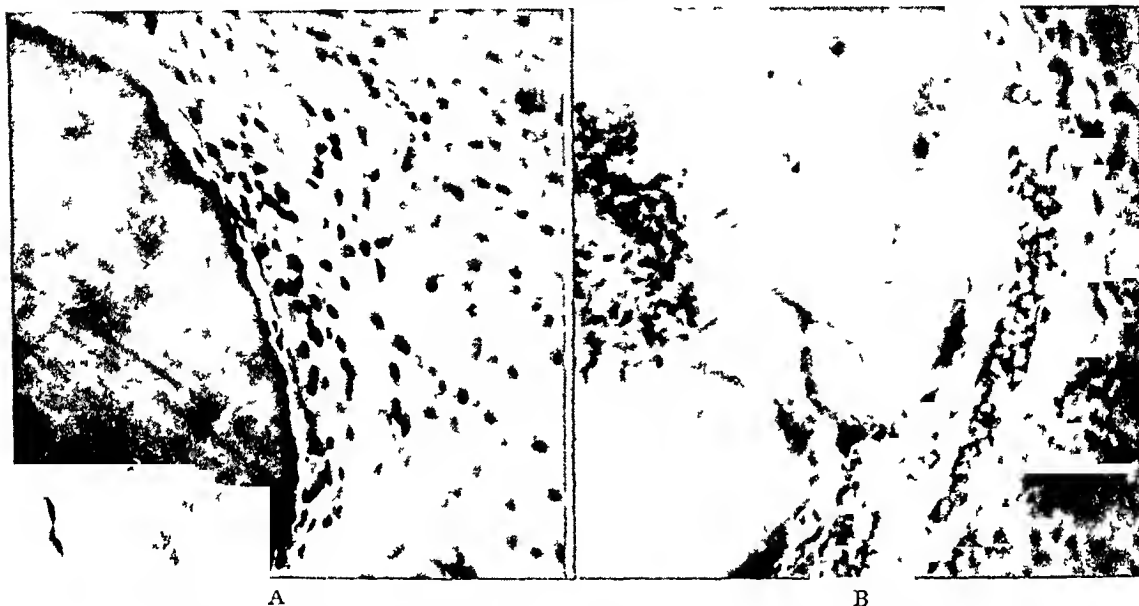


Fig. 3—Showing contrast in tissue response to No. 000 size of Type C—medium chromic surgical gut which was subjected to the washing procedure in 95% ethyl alcohol and subsequent drying before being implanted in the same animal. A. Product which was relatively free from hydrocarbon in the original tubing fluid and which did not elicit any appreciable polymorphonuclear leukocytic response. The macrophage fibroblast and lymphocytic response shown is the characteristic tissue response to relatively inert foreign material. B. Product which had 5%, or more, of hydrocarbon in the alcoholic tubing fluid which was apparently not entirely eliminated by the washing procedure, in view of the noticeable polymorphonuclear leukocytic invasion about, and even within, the catgut which is evidence of tissue irritation. (Digestion time in pepsin or trypsin of these two products were to a considerable extent comparable.)

The main point brought out in these implantation tests is that the irritating effect of the hydrocarbon in the gut may be substantially reduced in most instances by washing the suture in 95 per cent ethyl alcohol for 24 hours and subsequently eliminating the alcohol by evaporation or washing in saline. This procedure is not recommended for clinical use because of the possibility of introducing a factor of bacterial contamination of the suture.

COMMENT

In reviewing the literature on suture material and wound healing, one finds a considerable number of articles which deal with the superiority of silk, cotton, or stainless steel wire over catgut as ligature or suture material. These reports deal with clinical and experimental studies in which the authors found that wounds closed with catgut had more evidence of tissue reaction as evidenced by redness, induration, or serum formation, were more susceptible to infections, or were less secure than wounds closed with silk, cotton, or stainless steel wire.

Considerable interest in critical analyses of the healing of surgical wounds has been stimulated by the work of Whipple, Meleney, Harvey, Howes, and others. This has contributed substantially to improved technic and generally better wound healing in surgical cases.

In Whipple's⁵ report on the use of silk in the repair of clean wounds, he pointed out that there was a far larger zone of leukocytes about catgut implants in the abdominal wall of the rat than about silk, which appeared to indicate a more irritative reaction of the tissues to catgut than to silk. Meleney⁶ found that in experimental observations on dogs that catgut wounds contained more bacteria than silk wounds and, on the basis of this and a very extensive critical analysis of the incidence of infections and other complications in wounds closed with catgut or silk, concluded that the use of catgut favored the growth of organisms introduced at the time of operation.

Guthrie,⁷ in a clinical report on 470 surgical operations with silk technic, was convinced that silk had advantages over catgut because wounds healed with less tissue reaction, serum pockets seldom formed, and infections occurred less often in silk than in catgut wounds. Puestow,⁸ in a series of 100 thyroidectomies closed with catgut as compared with an equal number closed with silk, found that an advantage of the silk was a lower incidence of infection and serum drainage and better scars. Shambaugh,⁹ in his review of wound complications following herniotomy, found that the incidence of suppurative wound infections in the catgut series was twice that in the silk series. Also he found that minor wound complications such as hematoma or accumulation of serum were eight times as frequent in the catgut series as in the silk group.

Shambaugh and Dunphy,¹⁰ in their experimental studies on dogs, showed that operative wounds repaired with silk tolerate bacterial contamination better than similar wounds repaired with catgut. Cutler and Dunphy¹¹ reported on clinical and experimental observations on the use of silk in contaminated wounds and concluded that silk could be used in the presence of infection, and that the degree of infection in the immediate postoperative course was less than when catgut was used. Dunphy and Botsford,¹² in their report of a study of 600 thyroidectomies closed with silk or catgut, found that the incidence of nonsuppurative wound complications such as induration or serum formation as well as suppurative complications, was substantially reduced in the silk series as compared with catgut, even when it was used by meticulous technic.

In the work of Meade and Ochsner,¹³ which has stimulated the use of cotton suture material in many places, it was found that catgut produced the most reaction in the tissues and the slowest healing as compared with linen, silk, or cotton, the latter appearing to produce the least reaction and the earliest healing.

Babcock's¹⁴ reports on the use of alloy steel wire for ligatures and sutures has been responsible for the use of this material in a number of surgical clinics. In his observations on wounds closed with catgut as compared with

alloy steel wire, he felt that catgut produced reactions which retarded healing and favored infection. One observation which was made, which is quite pertinent, is that in testing catgut by implanting it in the skin he reported that this caused a red flare and a wheal in 24 hours which progressed up to a week, so that there was a zone of reaction and necrosis about each strand. This reaction is identical to that which was observed for xylene or hi-flash solvent when injected into the skin. Other favorable reports on stainless steel wire have been made by Preston¹⁵ and by Pratt¹⁶. Jones *et al*,¹⁷ found that the use of stainless steel wire in place of catgut in wound closure for abdominoperineal resections of the rectum had reduced the incidence of infections from 27.5 to 0.85 per cent. Disruptions after biliary surgery were reduced from 11 to 1.2 per cent. Kaufman *et al*,¹⁸ in their study of alloy steel wire, observed that during the immediate postoperative course there was distinctly less induration, redness and swelling of the tissues when wire was used than when other suture materials were employed.

In a description of disrupted wounds following closure with catgut, Falls¹⁹ noted "an inflammatory reaction characterized by excessive edema and outpouring of serum." Although an allergic phenomenon was suggested as an explanation, it is possible that this type of reaction could be caused by irritant hydrocarbons in the catgut.

The various reports which have been summarized bring out very clearly that there is an irritant factor in the use of catgut which is undesirable from the standpoint of optimum wound healing when comparisons are made with the various nonabsorbable suture materials. This irritant factor appears to manifest itself in the wound by induration, redness, serum formation, lowered tissue resistance with increased susceptibility to infection from organisms introduced at operation or from the blood stream and retardation of healing. The one point in common with the nonabsorbable suture materials which were used as a basis of comparison with the catgut, is that no extraneous irritant could be carried into the tissues with silk, cotton or alloy wire because these are simply heat sterilized in the autoclave and then prepared for use at the operating table. Surgical gut, however, has customarily been provided in glass tubes with either an anhydrous hydrocarbon liquid for boilable gut or an alcoholic solution for nonboilable gut. The anhydrous boilable tubing fluids have generally been xylene although in some instances may have been toluene. The alcoholic solutions of numerous products have been found to contain appreciable quantities of a hydrocarbon which is undoubtedly a residuum from the heat sterilization process which was not removed during the process of manufacture before the alcoholic solution was added and the tube sealed. Here, we have a common factor for the catgut, regardless of whether it was boilable or nonboilable which is the irritant hydrocarbon in the tubing fluid which our studies have demonstrated. In view of our observations presented in this paper it would appear that a fairly substantial part of the tissue irritation which these many observers have felt was characteristic of catgut when comparisons were made with the nonabsorbable

materials may be due to the irritant hydrocarbon carried into the tissues with the gut. The presence of alcohol in the gut from nonboilable tubing fluid or from dipping boilable gut in 70 per cent alcohol to induce pliability undoubtedly, contributes in part to the tissue irritation. It is our opinion that the action of alcohol is of secondary importance but not necessarily negligible.

The various reports on the use of nonabsorbable material as compared with surgical gut must be further evaluated, of course from the standpoint of size of suture material as well as the operative technic to arrive at a fair basis of comparison. Howes and Harvey²⁰ in their extensive work on wound healing and suture material have long stressed the importance of minimizing the bulk of suture material in wounds closed with catgut by resorting to the smaller sizes which they demonstrated to have adequate tensile strength in comparison with the strength of the tissues approximated. Their work has stimulated many surgeons to utilize a more meticulous technique using relatively smaller sizes of catgut which has resulted in a considerable improvement in clinical results with absorbable suture material. The minimizing of the bulk of suture material will of course decrease the amount of hydrocarbon introduced into the wound but would not eliminate this irritant factor. Dunphy and Botsford in their comparative series of cases where the catgut was used in relatively small sizes, by meticulous technic found that there was still an appreciable difference between the silk and catgut series.

Kraissle,²¹ in his review of suture material brought up the point of chemical irritants in the catgut which may contribute to tissue irritation such as the liberation of chromium; however in a subsequent personal communication he was of the opinion that xylene tubing fluid may account for the tissue irritation observed with boilable catgut.

Furthermore we believe that most of the excessive tissue reactions encountered in the previous work on the Absorption of Surgical Gut can be accounted for to a large extent by the irritant hydrocarbon factor of the tubing fluid. In reviewing the records of this work, it was found that the photomicrographs which portrayed the least evidence of polymorphonuclear leukocytic response of the tissues to the chronic catgut implants were from those products which were relatively free from irritant hydrocarbon in the tubing fluid according to tests carried out on tubes of catgut left over from these experiments. Also it was found that those products which were characterized by excessive exudate and profuse polymorphonuclear leukocytic invasion of surrounding tissues generally had a high hydrocarbon content of the tubing fluid. Furthermore some of the boilable products which were tested during this work but which were not reported in detail because the tissue reaction was so excessive that it was believed that some error in technic had occurred, undoubtedly derived their irritant properties from the xylene tubing fluid. In some of these tests the entire abdominal wall was edematous and the sinus tract where the catgut implant was located had the appearance of having been sealed by a cautery. Cultures of the exudate were usually

sterile. This chromic catgut usually disintegrated into shreds within a week or ten days.

In analyzing the action of the hydrocarbon in the tissues, it is probable that the excessive polymorphonuclear leukocytic response elicited by the irritant hydrocarbon contributes to a more rapid onset of the absorption mechanism. In the previous study, it was found that catgut was especially vulnerable to leukocytes. Whenever there was an excessive leukocytic response the catgut was generally rapidly absorbed, whereas catgut, which did not elicit an excessive leukocytic response, was generally absorbed over a long period of time by macrophages. On the basis of such observations, it was believed that there were two fundamental mechanisms of absorption—the leukocytic mechanism of rapid absorption and the macrophage mechanism of slow absorption. The former was associated with extensive evidence of tissue irritation; the latter with minimal irritation.

It is probable therefore, that the extraneous tubing fluid irritants induce a polymorphonuclear leukocytic response which hastens the onset of the mechanism of absorption. Once this leukocytic mechanism of absorption has started to break down the catgut it is not unlikely that the products of breakdown may further act as irritants to the tissues so that the irritation inaugurated by the tubing fluid may be enhanced or prolonged. The combination of these two factors may be important in the tissue irritation which has been observed with catgut. The elimination of the hydrocarbon irritant from the tubing fluid of chromic catgut is an important factor in obtaining relatively slow absorption by a predominantly macrophage mechanism, which is the characteristic tissue response to relatively inert foreign material. Even extensive chromicizing will not protect the gut from the attack of an irritant induced leukocytic response, which then breaks down the catgut by the rapid absorption mechanism instead of by slow absorption. Therefore chromic catgut which may be adequately chromicized by ordinary standards may undergo rapid loss of tensile strength and complete absorption before it has served its function of approximating tissues until strength from healing occurs if there is an extraneous irritant factor from the tubing fluid.

It was of considerable interest to find that the exudate which was formerly characteristic of many of the plain catgut implants was substantially minimized when these same products were subjected to thorough washing procedures. Plain catgut is more vulnerable to leukocytic absorption, and it is probable that a much smaller amount of irritant is required to induce the rapid absorption mechanism for plain catgut than obtains with chromic catgut.

SUMMARY

1. Weighing experiments have demonstrated that one to two per cent of the weight of boilable surgical gut was lost over a period of one to five days in a vacuum desiccator after elimination of the xylene tubing fluid on the surface of the gut. This weight loss probably represented the amount of xylene contained within the strand of gut. It is very doubtful that the usual

operating room procedures for inducing pliability of the boilable catgut, such as dipping in water or saline or 70 per cent alcohol would eliminate the xylene within the strand. Similar weighing experiments on nonboilable surgical gut have demonstrated that 18 per cent loss of weight occurred over a period of one to three days after removal of the catgut from alcoholic tubing fluid and subjecting the strand to stretching, as is customary in the operating room after removing the gut from the tube. In view of the observations previously reported by us, and Sidwell, that as much as five to ten per cent, or more, of the alcoholic tubing fluid may be composed of a high boiling range hydrocarbon it is assumed that the weight loss would account for a proportionate amount of this hydrocarbon. This would imply the presence of 0.9 to 1.8 per cent by weight of hydrocarbon in the catgut strand, which is comparable to the amount of xylene accounted for in the boilable gut.

2 Intradermal injection experiments in dogs and patients have demonstrated that 1 per cent, 0.5 per cent, and even 0.1 per cent emulsions of xylene or hi-flash solvent in saline will produce inflammatory lesions which are characterized by an initial capillary dilatation, edema, and subsequent leukocytic infiltration. These concentrations represented the injection of 0.43 mg., 0.215 mg., and 0.043 mg., respectively, of the hydrocarbons.

3 In correlating the weighing experiments with the injection tests, it would appear that the saline injections with one per cent hydrocarbon are comparable to the minimum concentration of hydrocarbon which was believed to exist in the gut under the conditions described. From the standpoint of actual amount of hydrocarbon, it should be pointed out that the intradermal injection of 0.043 mg. of xylene or hi-flash solvent was capable of producing an inflammatory lesion in the skin and that a single ligature of No. 1-size of catgut may contain more than twice this amount of hydrocarbon.

4 Implantation tests of surgical gut in the abdominal muscles of dogs demonstrate that the conspicuous tissue reactions which have been previously observed by us, and others, in the use of catgut may be substantially reduced if the catgut is thoroughly washed in 95 per cent ethyl alcohol and subsequently dried or washed in saline. This procedure did not always eliminate microscopic evidence of irritation, especially in such products as had a high hydrocarbon content of the tubing fluid. Elaborate washing procedures, however, are not recommended for preparation of catgut in the operating room.

CONCLUSIONS

1 The amount of irritant water-insoluble hydrocarbon from tubing fluids which in ordinary operating room technic may be carried into the tissues along with surgical gut, is adequate to explain a substantial part of such tissue irritation as has generally been attributed to properties of the catgut *per se*. The presence of alcohol in the gut from nonboilable tubing fluid or from washing procedures for boilable gut probably contributes in part to such irritation.

2 From the standpoint of obtaining optimum wound healing in surgery,

it is obvious that the introduction of tubing fluid irritants into the tissues along with suture material is not in the best interests of the patient or the surgeon

3 The elimination of tubing fluid irritants from surgical gut should result in generally better clinical results with the use of absorbable suture material

Appreciation is expressed to Lillian Eichelberger, Ph D, of the Dept of Medicine for her cooperation in carrying out the weighing experiments

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SURGICAL PRINCIPLES OPPOSED TO "RULE-OF-THUMB" IN THE TREATMENT OF COMPOUND FRACTURES*

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THE TREATMENT OF WOUNDS embraces a large part of the horizon of surgical interests at the present time. This, naturally, has been productive of marked increase in the number and range of investigative activities on the subject of compound fracture treatment. In studying the prolific literature in this field covering the last year or two, one is struck by the predominance of statistical analyses based on the effect of single factors in treatment. From the statistical side, some of the work has been very accurately, conscientiously and painstakingly done, with conclusions based on what mathematicians term "statistically significant figures." The punch-card system of analysis has been a great aid in the gathering of such actuarial figures. These may accurately indicate the percentage chance which a wound has of escaping infection under the routine use in a consecutive series of cases of a given procedure or a given combination of procedures. On the other hand, such data are of very doubtful value as criteria for the treatment of any given patient. Moreover, I feel moved to question seriously the wisdom of attempts to establish procedures for routine application in the treatment of compound fractures. No matter how sound the statistical basis for the conclusions drawn as to the percentage of success which may be expected from the routine employment of a given therapeutic procedure *in a large series of cases*, the adoption of that procedure as a routine automatically dooms to failure, from the outset, a certain percentage of them. To make such data of clinical value in the treatment of the *individual case*, it is of vital importance that we know when *not* to follow a procedure which is ordinarily successful. In other words, it is essential that we employ no procedure which has a percentage of failures as a routine, but that we establish criteria enabling us to judge as to when its use is sound or unsound, in order to eliminate, insofar as possible, the failures inherent in the use of a routine procedure. This cannot, unfortunately, be based upon the study of individual factors. Every compound fracture presents a closely knit combination of a large number of factors which must be considered, so to speak, as a word, not as a group of letters. A given group of letters can give a great many different answers in the way of words dependent upon the arrangement and relationship of the letters. Our interest must be in what the letters spell as much as in what they are. The possible combinations of the large number of factors encountered in the treatment of compound fractures are numerous and widely varied. If all the permutations of such combinations could be accurately plotted, with an indicated course of procedure for each permutation, there would be no need for such things as surgical judgment or surgical principles.

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We could then have *rules* for treatment. I have no doubt that this might be a mathematical problem capable of solution, but it would entail a statistical study somewhat astronomic in proportions and bewildering in its complexity.

I have no doubt that at least some of the studies being made on the effects of individual factors in treatment are planned as preliminaries to studies of the effects of various combinations of factors and on the interrelationships of those factors. This tends to lead to the weltering complexity of statistical study suggested above. Unfortunately, and I am certain, contrary to the desires of some of those making such preliminary studies, the statistical data to date are being too generally interpreted in terms of rules for action. When a statistical study of the results of wound closure in compound fractures is announced showing that, in a given series, a higher morbidity to infection was observed in those left open than in those closed, the popular interpretation is apt to be in terms of the dictum "close your compound wounds." The statistical results in a series may continue to be favorable following such a rule, but the results to certain individuals in the series are disastrous, although it may well be that the author had neither the intention nor desire to have his statistics so interpreted. Similar rather general false interpretations, for instance, have resulted from statistically accurate findings that extensively "debrided" wounds show a higher morbidity to infection than do those minimally "debrided," and that wounds in which extensive or prolonged lavage has been used show a higher rate of infection than do those in which little or no lavage has been used. Another way of interpreting such findings might be, perhaps, that wounds of such character and extent as to call for extensive debridement and lavage are apt to show a higher morbidity to infection than those not requiring such treatment. This, of course, is quite a different viewpoint.

Have we any criteria, apart from statistical studies, on which to base the procedures to be used *in the individual* case, and are those criteria a sounder basis for the treatment of the individual than such statistical data as we have indicated above? I believe the answer to both questions is in the affirmative, and that the criteria are what are known as surgical principles, and that the role of statistical study should be principally to analyze the failures of any given procedure from the standpoint of what surgical principles were violated in the use of the procedure in those cases. If our accepted surgical principles are wrong, we should abandon them, and should evolve and adopt other criteria which permit us to decide as to what is the best thing to do for the problem presented by the individual patient, rather than criteria which determine what procedure can be used in a large series of cases with the least number of preordained individual failures.

I believe that a logical analysis of the whole problem allows us to establish relatively simple criteria on the basis of which we can decide in the individual case what procedures should be used, and how they should be used. Such an analysis is no more than a review of established surgical principles and standards and their bases. Of this I am well aware but it appears to me

not only timely, but a sober and steadying influence which may not be amiss. It should embrace discussion of

- 1 The problem presented by a compound fracture
- 2 The necessity for regarding the wound and the fracture as parts of the same problem
- 3 The necessity for dealing with both these problems simultaneously at all times
- 4 What it is desired to accomplish for the wound and for the fracture by the procedures employed
- 5 The basis for decision as to procedures to be employed in any individual case
- 6 The procedure now in common use or advised for common use from the standpoint of the accomplishment of treatment aims

1—THE PROBLEM PRESENTED BY A COMPOUND FRACTURE

This may be very simply stated in broad terms. The problem is that of preventing the *translation* of contamination into clinical infection if possible, the minimizing of the damage done by infection if it develops, the healing of the damaged tissues in as short a time as possible with a minimum of residual tissue disability and deformity. All the indications for therapy to bone and soft parts are contained in this statement.

2—THE NECESSITY FOR REGARDING THE WOUND AND THE FRACTURE AS PARTS OF THE SAME PROBLEM

This is a vital viewpoint in the formulating of sound principles for treatment in compound fractures. There is often a distinct tendency to regard the wound of the soft parts and the wound of the bone as different problems requiring separate consideration. Nothing could be more deterrent to sound and logical consideration of treatment. The soft part lesion cannot be treated as one entity in accordance with certain principles and standards, and the bone lesion as another and separate entity involving the employment of different principles and standards. This is true whether considering the problem from the standpoint of infection, of wound healing, or of residual disability or deformity.

3—THE NECESSITY FOR DEALING WITH BOTH THESE PROBLEMS SIMULTANEOUSLY AT ALL TIMES

It is essential at all times to regard what is being done as being done for the whole wound and to view each procedure used from the standpoint of its effect in meeting the general problem in both bone and soft parts. The viewpoint that our first or major consideration should be the question of infection in the soft parts may lead to deplorable results in the bone lesion. The viewpoint that the accurate reduction of the fracture is the essential feature of treatment may lead to regrettable soft part complications. The realization that the treatment of both bone and soft parts is based on the simultaneous application of the same principles to both lesions at all times

leads to a minimum of residual damage in both. This essential viewpoint is brought out in the discussion of procedures which follows.

4—WHAT IT IS DESIRED TO ACCOMPLISH FOR THE WOUND AND FOR THE FRACTURE BY THE PROCEDURES EMPLOYED

This is, in effect, the answer to the question "How do we attempt to meet the problem stated under 1, above?" We may express our desires and the reasons for them as follows:

If the Lesion is in the Stage of Contamination

a For obvious reasons, to remove as much of the contamination as possible, *and to add* as little as possible. We must realize that we cannot remove all contaminating organisms, and that the tissues have to deal with those left behind.

b To remove as much dead and obviously devitalized tissue as possible with as little additional damage as possible. Dead and devitalized tissue acts as a culture medium to furnish pabulum for the organisms left behind. Through the local accumulation of products of its autolysis it is a definite handicap to the biochemical progress of bony healing in fracture. Primary fracture healing must be conceived of as taking place in the tissue immediately surrounding the fracture rather than from bone-end to bone-end, and optimum conditions for primary fracture healing demand the presence of living vascular tissue for the production of the undifferentiated connective tissue about the fracture site which is the medium for so-called primary callus formation. From the standpoint, then, of both wound and fracture healing, as well as from the standpoint of minimizing the chances of *translation* of contamination into infection, the elimination of dead and devitalized tissue insofar as is possible is a sound desideratum.

c The elimination insofar as possible of dead spaces within the wound. This is a principle accepted as sound in all other surgical procedure. It should be sound here. It involves not only the surgical exposure and elimination of dead spaces where indicated but also particularly meticulous hemostasis—the approach to a dry wound—to obviate the creation of dead space containing pabulum for bacteria by the formation of subsequent hematmata. As adequate a reduction of the fracture as is possible is an obvious corollary of this principle, if it be sound.

d As adequate and accurate a closure of the wound as is possible without the creation of tension within it at the time of closure *or subsequent to the time of closure*. The closure we desire to shorten the healing time, to minimize the subsequent scarring and deformity, and to minimize the opportunity for subsequent additional contamination of the wound. The principle applies to the closure of the bone portion of the wound—*i e*, fracture reduction—as positively as it does to the soft part of the wound. We desire to avoid tissue tension because we believe that its existence leads to impaired wound healing, and to impairment of the tissues' ability to deal with the organisms still remaining in them. In addition, tension in the soft parts surrounding the bone seriously impairs the minute circulation therein—

the circulation of the fluids in the tissue spaces, the lymphatics, and the ultimate capillaries. It is this circulation which is of such vital importance in restoring, after injury, the biochemical status in the tissue fluids which is essential to the deposition of calcium in the healing tissue about bone to form callus. From the dual standpoint then, of preventing the *translation* of contamination into infection and of promoting bone and soft-part healing, the development of tension within the tissues of the wound must be prevented at all times. From this standpoint, the accuracy of reduction of the fracture itself—i.e., the closing of the bone wound—must be considered from the standpoint of the degree of violence necessary to attain complete and accurate reduction in terms of resultant tissue damage, inflammatory reaction, and resultant tension within the tissues. Complete fracture reduction, simultaneously with complete wound closure is ideal and desirable. The real question to be answered in the individual case is to what degree is it wise and safe.

Rest of the wound until the risk of *translation* of contamination into infection has been passed, and until the healing of the wound has been adequately initiated. This applies, if the principle be sound, equally to both soft parts and bone as part of the same problem, although chronologically the answers to the two are different. Rest of the noninfected wound in the soft parts until healing is adequately initiated is a question of days. Rest of the noninfected wound in the bone, on the same basis, is a question of weeks. The necessity for contaminated bone and soft-part wound rest, until the period of infection risk is passed and until healing in each is adequately initiated, is absolute. The ideal treatment would allow of functional activity of the soft parts and bone, if possible, simultaneously at the early date. It is possible by some methods of treatment for the bone wound to accomplish an approach to this ideal. To be safe and successful they must maintain rigid fixation of the bone fragments—i.e., bone wound rest—until the healing of the bone wound is safely established—i.e., until callus formation is adequate to maintain the edges of the bone wound from separating—while functional activity of the extremity is being carried out. Rigidity of fixation of the bone fragments in compound fractures, because of this factor, is even more important than in the simple fracture. I am certain that mobility at the fracture site is a potent factor in determining whether or not contamination in compound wounds is *translated* into infection and whether or not the bone is involved seriously if infection does develop.

If the Lesion is in the Stage of Infection

Treatment of these wounds is on an entirely different basis from that governing the treatment of contaminated wounds. The surgical principles underlying the treatment of infection are to provide adequate drainage with the elimination of pocketing to remove any foreign material present, to avoid opening up channels for spread of infection, to provide rest for the wound until the infection is adequately controlled, and to provide the patient with whatever aid we can to enable his tissues to control it. These principles again apply equally to soft-part wound and to bone wound, and, obviously

and grossly, modify our procedure. No question here of debridement as hereinafter defined, no question of closure.

5—THE BASIS FOR DECISION AS TO PROCEDURES TO BE EMPLOYED IN ANY INDIVIDUAL CASE

a. Is the case contaminated or infected? In some respects this is a good deal like asking the question "How long is a piece of string?" However, there are certain definite things one can say. In the first place, all compound fractures are either one or the other, whether the compounding has occurred from within or from without. If they are considered contaminated they should be treated as contaminated cases. If they are considered infected they should be treated as infected cases. Too often, the procedure adopted attempts to split the difference, or the wound is considered neither infected nor contaminated—a dangerous attitude to assume. The extent of the procedure followed must be influenced by a number of factors. The number of hours elapsed between time of injury and time of wound treatment is by itself an inadequate criterion as to the probable status of the wound. The circumstances under which the wound was received (to include the locale, possible types of contamination, the probable habitual condition of cleanliness of the patient's skin and clothing covering the wounded region), the type and severity of the violence and the amount of tissue damage present beneath the skin and subcutaneous tissue rather than the size of the skin wound, the adequacy and promptness of the first aid treatment accorded both soft-part and bone wounds, all these must be considered in addition to the actual lapse of time in deciding the question in terms of wound pathology.

Each of the possible combinations of these various factors has a different significance in determining whether or not the lesion should be viewed as contaminated or as infected, and, therefore, as to what principles should be followed in handling it.

The amount of tissue removal to be practiced in a given contaminated case must be determined by not only the amount of tissue damage present, but by the nature of the damaged tissue and the potential disabilities or risks occasioned by its removal, the amount of gross contamination present, the press of time by reason of the patient's condition, or by reason of other factors at times encountered—particularly in military surgery—and by the region of the body involved. Upper and lower extremity wounds differ remarkably and radically in respect to healing characteristics and morbidity to infection, although all other factors involved may be apparently identical.

The extent to which the wound may have to be extended will be governed by the size and location of dead spaces, by the evidence of tissue damage and contamination, by the necessities of adequate hemostasis, and by the difficulties to be encountered in wound closure.

The necessity for cleansing, but nonirritating lavage of the wound, and the amount of such lavage, will be governed by the size of the wound, by the amount of gross contamination originally present, and that, of necessity,

COMPOUND FRACTURES

left behind after tissue removal, by the presence or absence of foreign bodies within the tissues, by the number of clots encountered and by evidence of contamination having been carried into the depths of the wound

The degree of accuracy of reduction of the fracture, and the method employed in attaining it, must be governed by the nature and location of the bone injury, by the time available for the procedure, by the amount and significance of the additional trauma inflicted and by the equipment and assistance available for carrying it out. The method to be employed in the individual case is that method which, under all the particular circumstances, will come nearest to an ideal of "wishing" the fragments into satisfactory position. And no matter what method is used, it must be employed with this object in mind and not merely with the object of restoring bony anatomy as evidenced roentgenologically. This is the closure of the bone wound, and it should be governed by precisely the same principles as closure of the soft-part wound.

The closure of the soft-part wound must be governed by evidence of the creation of tension at the time of closure, the creation of tension later by reason of inflammatory swelling in the tissues, the degree of hemostasis obtainable at the time of closure and immediately thereafter by pressure dressings, *etc*, the degree and type of contamination present originally and after wound toilet, the amount of dead and devitalized tissue left in the wound, the presence or absence of foreign bodies and the necessity or advisability for coverage of structures which, uncovered, do badly (such as tendons, nerves, periosteum stripped of soft parts, and the actual site of fracture). Exposed periosteum, stripped of soft-part attachment or coverage, acts much like exposed tendon.

The degree and extent of time to which rest of the soft-part portion of the wound must be employed is dependent upon local circulatory factors, on the degree of healing necessary to permit functional activity of the particular soft parts involved and on the tension to which that soft-part healing is subject by reason of difficulties of closure, rather than by the length of the wound, in addition to the time necessary to be reasonably certain that the contamination left in the wound has not been *translated* into infection. The fact that wounds heal from side-to-side and not from end-to-end, is of importance in this respect. The degree and extent to which rest of the bone portion of the wound must be enforced by immobilization of the whole portion of the body involved is dependent upon the availability of equipment and skill for the carrying out of the various methods employed. In general, that method is most advantageous which allows of the greatest degree of voluntary muscular activity without endangering the rigidity of fixation of the bone fragments at the fracture site. The healing of the fracture site is the bone wound healing, and the wound edges must be kept at rest until the healing is sufficiently established to stand the strain of functional activity. On the other hand, there is no question but that voluntary activity of the *muscles* of the part is a potent factor in determining the probability and

speed of progress of bone healing, provided the bone fragments are at rest. In the employment of any method, then, one must aim at securing the maximum of voluntary muscular activity consistent with rigidity of the fragments at the fracture site—no more and no less.

6—THE PROCEDURES NOW IN COMMON USE OR ADVISED FOR COMMON USE FROM THE STANDPOINT OF THE ACCOMPLISHMENT OF TREATMENT AIMS

Emergency or First Aid Treatment

To properly aid in the carrying out of sound principles of treatment this should be applied as soon after injury as possible without adding to, or more widely distributing, the wound contamination already present and should protect the wound from further contamination and should control hemorrhage. It should render and keep the injured soft parts and bone as quiet as possible until definitive treatment is undertaken, and should inflict as little additional trauma as is possible. Abstinence from washing about the wound or the use of antiseptics as first aid measures is indicated. The prompt covering of the wound with adequately protective sterile dressings, of the pressure dressing type if necessary to control hemorrhage, is indicated. Tourniquets are contraindicated unless pressure dressings fail to control bleeding. As extensive immobilization as possible, preferably with the employment of constant fixed traction, is indicated. As regards the prophylactic use of chemotherapy, locally and by mouth, there would seem to be certainly no contraindication provided that if used locally in the wound it is as a thin film rather than in large masses and provided that by either mode of administration it is not relied upon to make it safe to delay definitive wound treatment. By the at present available data chemotherapy must be used as a hope in the event of unavoidable delay and as a hope in the attempt to prevent local or general sepsis. It must as yet be regarded as an adjuvant to surgery, and not as a substitute for it. I do not believe its use warrants the abandonment, in any respect, of what have, up to now, been considered sound surgical principles or of the procedures properly employed to carry out those principles.

The Employment and Character of Wound Debridement or Wound Drainage

I must preface my discussion of this point with an apology to purists for my use of the term "debridement" in describing what I have in mind. I am aware that the term in its strict and literal sense does not embrace all that I use it to describe. By debridement I mean the removal of dead devitalized and contaminated tissue from a contaminated wound with the elimination of dead spaces and foreign bodies within the wound. To be justified, débridement must be undertaken for a contaminated wound, and it must remove as much of the affected tissue as possible and eliminate dead spaces and foreign bodies, in keeping with the principles previously stated. A so-called debridement which does not accomplish this, or one which distributes contamination more widely which removes clean and viable tissue which inflicts an appreciable amount of damage in the doing or which

creates dead spaces within the wound is insult added to injury. It is not good surgery. In an infected wound, as gauged by the probabilities evaluated heretofore, drainage should be adequate for the infected area, preferably dependent, should attempt no removal of tissue other than surface contamination, and should remove foreign bodies when possible. Invasion of sound tissue violates principles.

Lavage of the wound should have for its purpose removal of contamination from the wound. To accomplish this it must proceed from the base of the well-retracted wound, with sufficient head to give a visible and forceful flow from the depths outward. The amount of saline used (and saline is adequate) is far less important than the rate and force of flow. A lavage so conducted that the fluid lakes in the wound, with little if any force of flow, serves probably to generally distribute what contamination is present. It is obviously not carrying out the principle involved. One might make the comparison between the cleansing effects of a tub bath and of a shower. In a tub bath the individual laves all parts of his body in the contamination from all other parts, in a shower he washes the contamination from his body. Lavage of a wound should have the effect of a shower from within not of a tub bath.

Local chemotherapy following this wound toilet must be subject to the same restrictions as mentioned in discussing its prophylactic employment. I do not believe there is at present justification for altering the surgical criteria for wound closure in any respect because of the use of chemotherapy on the basis of the data now available. Systemic chemotherapy is justified, but only on the same basis with the added warning that severe kidney and liver damage can result not only from overdosage, but from extremely moderate and short-lived dosage in susceptible individuals.

Wound Closure—Soft Part

No one can deny the advantages of a closed wound over an open one from the standpoint of wound healing time and character, the minimizing of secondary contamination, and from the standpoint of aid in the bone healing process. Tension, at the time of closure, or later, is a definite threat however, which may far outweigh these advantages. The degree of tension to be risked must be based upon an evaluation of the various factors listed under the principles involved in wound closure as present in the individual case. The use of releasing incisions of flaps, and other plastics must be considered and may be of advantage in securing closure without tension. The use of elevation and of pressure dressings may be of distinct aid in preventing intratissue tension during the inflammatory reaction in the subsequent days. When, however, primary closure entails a degree of tension which, in the individual case, is a definitely recognized, or even probable, risk, I feel strongly that it requires considerable justification. The placing of untied sutures with a view to a delayed closure guided by the same principles when, and if, the wound has proven clean, or no closure at all is, I believe a safer and sounder practice, more in keeping with surgical principles.

Wound Closure—Bone

The bone wound should be closed—that is, the fracture should be reduced—at the time of soft-part wound closure. It should be accomplished to the maximum degree possible without violating the principles laid down previously, and by the method which under the circumstances of equipment and personal skill is apt to inflict the least damage commensurate with reduction adequate for the part involved. It is unsound thinking to label one method as universally preferable to another. Familiarity with all the potentialities of a theoretically inferior method combined with the skill and armamentarium adequate to *translate* those potentialities into fact are far more important factors than the theoretic excellence of a method in the absence of similar familiarity, skill, and adequate armamentarium in deciding the method to be employed in carrying out fracture reduction that is sound in principle. The essential thing is that no matter what the method used it must be used to its maximum efficiency in putting those principles into practice.

The same commentary holds true as to the methods to be considered for giving rest to the bone wound—fracture fixation or immobilization. No matter what the method used, it should be employed so as to exert, to the maximum its potentialities in giving rigid fixation or rest to the fracture site or bone wound, until the bone healing process is capable of functional strain and it should employ, to the maximum degree possible, voluntary muscular activity as soon as fear of *translation* of contamination into infection has passed and the soft-part wound healing is capable of standing the strain of functional activity.

Time does not permit of the detailed evaluation of the various methods of fracture reduction and fixation from the standpoint of their mutual theoretic advantages and disadvantages. That they one and all, should be used to carry out, to the greatest degree possible, definite principles is the essential feature for the successful use of any of them.

DISCUSSION—DR FRANK L. MELENEY (New York) Doctor Murray has obviously directed his criticism at the statistical study of contaminated wounds, the results of which have been reported (ANNALS OF SURGERY, 118, 305, August 1943). If one goes about *trying to prove* something by means of statistics, I admit that figures can be distorted so as to simulate proof but if one goes about *trying to find out* something, statistics may be of real value. This we have tried to do.

Statistics so studied are more likely to bring out and support principles than they are to lay down “rules-of-thumb.” “Rules-of-thumb” are characterized by having no weights or measures. They are what a cook uses to bake a cake, and a good cook can make a good cake, and a bad cook, a very bad cake by “rules-of-thumb.” But that is precisely what statistics are not. Summary sheets which attempt to cover all of the factors involved in a given problem permit more or less precise measurement of these factors, and punch-cards which permit cross tabulations permit an evaluation of the relative importance of the various factors involved. Figures so obtained must then be subjected to the formulae of the biostatisticians in order to rule out the element of chance.

Under these circumstances, if statistically significant figures are obtained which seem to conflict with a principle, we must study the matter carefully to find out if it was really a principle or a preconceived notion.

Doctor Murray has been a student of fractures for many years and has worked out certain principles for their treatment which I will not question. But during the past year, while he has been directing one of our units studying compound fractures, he has seen more compound fractures than in all of the ten years preceding. And I know, for a fact, that he has modified some of his methods of treatment, and I believe he has modified some of his ideas about them, perhaps not as a result of our figures as much as the result of his own experience. If he had not learned something during the past year I would have questioned the elasticity of his cerebral arteries.

It is a duplex if not a complex problem. It combines the problem of the healing of the bone and the problem of healing of damaged soft parts in the presence of bacterial contamination, the nature and extent of which the surgeon does not know when the case comes to his hand. The sooner he does know that the better will he be able to evaluate the possibility of his attaining his purpose of getting bony union and soft part function and of preventing infection. The underlying principles directing the surgeon to accomplish the desired end-result with regard to healing of the bone and the free movement of surrounding muscles and neighboring joints may be in conflict with the principles underlying the prevention or treatment of infection. Frequently it is necessary to compromise one principle to gain the other. For example, to get good alignment and approximation of bone ends it is important to preserve as much of the bone as possible. However, badly contaminated bone ends or detached fragments may be retained when, from the point of view of infection, the contaminated bone and loose fragments should be removed. Similarly, the insertion of a foreign body, like a metal plate and firmly driven screws, may immobilize the bone fragments but carry organisms deeply into the bone and cause necrosis of bone around screw-holes or next to the plate. There is always some bone necrosis around skeletal traction wires or pins or skeletal fixation pins, and necrotic tissue is a fertile soil in which infecting organisms may gain a foothold. The desire to obtain early function of surrounding muscles and joints may urge early motion when, from an infection standpoint, immobilization of both joints and muscles would seem to be indicated.

Recently, another factor has come in which must be considered and evaluated, namely, chemotherapy. That may involve a conflict of principles. The new drugs may inhibit bacterial activity and, at the same time, interfere with wound healings, act as foreign bodies, or change the metabolism of the tissues so as to materially delay bony union.

It is only by studying the cases as a whole as well as individual cases, trying to measure and weigh as accurately as possible the result and the effect of these new agents of treatment, that we can gain knowledge which will further improve our results in this interesting and complicated field of surgery.

DR CALVIN M. SMYTH, JR (Wynnewood, Pa.) It is a relief to hear somebody reemphasize the fact that general surgical principles have not been thrown out of the window by the introduction of chemotherapeutic measures.

Two years ago, before this Association, I had the privilege of discussing Dr Philip Wilson's paper on compound fractures, and, at that time, I had occasion to say that we had been using the closed plaster encasement treatment of compound fractures for some fifteen years and that, while during the past two years we had introduced sulfa drugs into the wound in the treatment of compound fractures, we had failed to see any difference in the results that we obtained since the introduction of sulfa drugs over the results we obtained previously.

I am glad to say that we have the courage of our convictions, and for the past year have introduced no sulfa drugs into the wounds of compound fractures that were brought to definitive surgery within the time limits ordinarily accepted for debridement.

I want to thank Doctor Murray for bringing this matter before the Association, and I think that a few contributions of this sort will serve to prevent the treatment of compound fractures and wounds from being turned back seventy-five years. Certainly there were heroes before Agamemnon, and heels before Achilles.

DR FRASER B GUNN (Montreal, Canada) I want to support what Dr Calvin Smyth has said in reference to the value of Doctor Murray's contribution. I am not quite sure that seventy-five per cent regression might take place, but the unquestionable surgical principles must hold if we are to treat wounds in this war and in industrial and road accidents, and during and following the war.

At the risk of perhaps appearing to be facetious, I shall read over ten principles, as I see them, that make for adequate wound healing, whether such wounds be associated with fractures or not. They are all as you will notice, based upon the letter 'E'. If any one of these features is not possible, difficulties are certain to arise later in the course of the individual case.

(1) Early operation, (2) enlargement of the wound in order that interstitial tension may be overcome and prevented, that (3) exploration of the wound may be adequately carried out, that (4) extraction of foreign bodies may be brought about, (5) excision of devitalized tissue may take place, (6) the exhibition of germicides and bacteriostatics, (7) the establishment of (cutan) drainage, (8) encapsulation of the part for the exclusion of secondary infection, (9) efficient immobilization, whether that be by plaster or by other means, and (10) the elimination of frequent dressings.

DR WILLIAM DARRACH (New York, N. Y.) I do not want to discuss principles and I do not want to discuss statistical methods. I do not want to discuss chemotherapy. I would like to bring out what our main objectives are in treating compound fractures.

First and foremost, comes the saving of life. Second comes the eventual return of function to the highest possible degree. Third comes the cutting down of the period of disability.

If we try to lay down flat rules, which will be followed under all circumstances, we are lost and beaten at the start. I think today, with the problem brought to such great importance because of war conditions, the question of surgical judgment is brought into play much more than it is in civilian work.

In civilian work, Albert Key, and a few other lucky men, can close all their compound fractures. Under battle conditions I think very few can.

In applying surgical principles we have to use horse-sense and surgical experience to the nth degree. The multiple factors that enter into a decision, which must be made without bacteriologic evidence, because that is lacking at the time of the primary operation, require everything that we can put into it.

Some of these factors are: The condition of the patient at the time he was injured, the condition of his skin and the parts of his clothing; of the terrain, of the injuries associated with that compound fracture, with the time elapsed since his injury, the kind of the first-aid treatment he had, from the time he was hurt until he came into the operating room, the amount of immobilization he had during that time, and the amount of time that can be spent by the surgeon on that individual case, which will depend on whether the case comes to him in a quiet lull, when he can spend all the time he wants, or whether he is rushing through a large batch of wounded.

Those are simply a few of the factors which must enter into the primary decision as to just what you are going to do at the time with that individual case. How are you going to save his life? How are you going to give him a serviceable leg or arm? How long is he going to be disabled?

I think unless we have something to fall back on, besides a flat "rule-of-thumb," whereby we have to "use our beans," we are not going to give these boys a square deal. For that reason, I think that if we can learn and understand and then apply, with surgical judgment, fundamental principles, we will get farther than if we try to treat them all by some flat rule.

DR CLAY RAY MURRAY (New York, N. Y. closing) There is little to say in closing this discussion except to reply to some of the comments made.

It is perfectly true as Doctor Meleney has stated, that we have introduced some changes in procedure into our treatment of compound fractures at the Presbyterian Hospital since this study began. These changes were introduced in order to aid the

study and not because of change in our attitude. As a result of a year's experience with those changes I am firmly convinced that the major ones were ill-founded and should be discontinued.

As regards the use of chemotherapy it can be safely said that there has been, to date, no convincing evidence to prove that the introduction of chemotherapy into a compounding wound has exerted any influence on the morbidity of such wounds to infection. The original report of the cases at Pearl Harbor made strong claims in this regard, but subsequent developments in the same cases have cast a great deal of doubt on the validity of the original reports.

On the other hand, there is no convincing proof that chemotherapy intelligently employed locally has done any harm to the patient. It has been claimed that local chemotherapy interferes with wound healing, but it is considered probable that ill effects on wound healing have, at least in many instances, been due to the use excessive amounts rather than to the action of the drug itself. Basing our opinion on the consensus rather than on the opinion of any one investigator we must conclude that there has been no conclusive evidence adduced to support the idea that local chemotherapy is harmful. I can therefore see no objection to its use—in fact, I think it should be used. I think, however, that it should be used as a hope and not as a reliance, and most certainly not as a substitute for the adequate carrying out of sound surgical principles.

Debridement, as the term is commonly understood, and lavage have been brought into serious criticism by some investigations. Debridement is designed to remove dead and devitalized tissue, to remove contamination, and to eliminate dead spaces in the wound. If done so as to carry out these purposes the procedure is sound. If, on the other hand, it is so carried out that infection is carried into the depths of the wound and extensive tissue damage is inflicted, it should not be done. Lavage of the wound has been criticized because statistical evidence seems to show that those wounds which are extensively lavaged have a higher rate of infection than those less extensively lavaged.

This can be stated in quite a different way, as I have noted in the paper. There is, however, this additional point to be considered in lavage. The procedure is supposed to remove contamination, not to introduce it. In considering this factor, one might stress the comparison between a bath and a shower. When an individual takes a tub bath he merely assures himself of the fact that he has evenly distributed all over his body the contamination present on any one part of his body. When he takes a shower, on the other hand, he washes from his body all contamination. If a wound lavage is done using a low head of pressure for the solution so that the fluid stays laked in the wound for the most part, and if the tube introducing the fluid is placed in the superficial parts of the wound, the procedure may introduce and distribute infection—it is a wound tub bath. If the lavage is done with a soft rubber catheter carefully introduced to the depths of the wound and with a head of pressure sufficient to produce visible forceful and outward flow of the fluid, it removes contamination from the wound—it is a wound shower from within.

I should like to say that the thoughts expressed by Doctor Darrach have been considered in the paper as prepared for publication not only in regard to the principles involved but in reference to the rationale by which methods of treatment carry out these principles. The emphasis should be placed on the principles to be carried out rather than on the method by which they are carried out. The tendency is to place stress on the routine use of a method. A method of procedure which will produce satisfactory results in 90 per cent of the cases on which it is routinely used excites in me the most heartfelt sympathy for the unfortunate ten per cent who are doomed to failure from the beginning by the routine use of the method, and who are statistically insignificant.

THE MEDICAL TREATMENT OF HEMATOGENOUS OSTEOMYELITIS⁺

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THIS ACUTE DISEASE of childhood and adolescence and, infrequently, of adult life, is mainly due to staphylococcus or streptococcus. Of the two organisms, staphylococcus caused over 90 per cent of all cases in this and other series¹. The organism gains entrance to the blood stream through lesions of the skin, of the mucous membrane, or the tonsils. The blood becomes contaminated and the organisms are deposited in certain areas of the body. It has been shown experimentally that viscera, muscles and bones may develop abscesses. In bone the areas involved are the epiphysis, the metaphysis, and the periosteum. There has been much work done to explain the occurrence of abscesses at these situations^{2, 3}.

A study of the autopsy records of patients dying of this disease shows the same distribution of abscesses as in the experimental animals dying of it (Table I). The picture presented is that of a general infection. Heart,

TABLE I

RESULTS OF AUTOPSY IN 51 CASES OF ACUTE OSTEOMYELITIS

Total number of autopsies	51
Acute pericarditis	3
Acute pleurisy or empyema	10
Abscesses or infarctions in lungs	22
Abscesses in kidneys	16
Acute arthritis	9
Metastatic osteomyelitis	4
Subcutaneous and intermuscular abscesses	9
Abscesses in myocardium	7
Abscesses in thyroid gland	1
Abscesses in spleen	1
Abscesses in prostate	1
Abscesses in liver	2
Acute duodenal ulcer	1
No pyemic lesion found	6

kidneys, liver and spleen are involved with inflammatory areas. The lung has areas of patchy pneumonia, and thrombophlebitis is prominent in all lesions. In view of these findings it is strange to think of osteomyelitis as a local surgical condition, and it is, therefore, rational to look for an agent that will assist in preventing this appalling chain of full-blown septicemia. We have all been familiar with the treatment of the recent past. First and always surgical interference with the local lesion as soon as it could be identified, later, interference, perhaps when an abscess could be identified the while the patient had supportive treatment with fluids, *etc*. We have gone through a stage of giving antitoxin. But the mortality records prior to the adminis-

⁺ Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

tration of sulphonamides was about 22 per cent in our series. On the whole the results were poor from the mortality standpoint. There are apparently no records of the mortality rate in cases of osteomyelitis that did not have the benefit of surgery! Yet we have all seen the late case, one that has survived the early acute phase and has come to hospital with a single lesion, either undrained or opened spontaneously. We have seen, too, the case of Brodie's abscess, unrecognized in its formative stage, but discovered and recognized as a lesion of the bone years later. Such cases amply demonstrate nature's ability to deal with the acute phase of osteomyelitis in such a way as to prevent a fatal issue, and indeed alone and unaided, to cure the disease. I strongly suspect that so-called undiagnosed and untreated cases would show no such mortality as 20 per cent.

What are the methods used by nature to subdue this invasion? Ninety per cent of the deaths in the past have occurred in the first and second weeks. The natural antitoxin developed as a reaction to toxin is useful in dealing with the toxin elaborated, but has no effect on the extermination of the invader. The human organism kept from being overwhelmed with poison, is capable of producing and maintaining agencies, phagocytes, bacteriolysin, *etc.*, that directly attack and destroy the invader. While this conflict is progressing the patient afflicted has all the signs of a reaction and until the balance is well in favor of the defence that reaction is very obvious, both generally and locally. From then on there is no real reason why the defence should not greatly increase its power so that the general invasion is wholly under control. The whole system of defence is apparently predicated upon the extermination of the invader or at least containing him until protective substances can be developed and he can be brought under control. The work of Leveuf⁴ gives a good record of a supervised, non- or late interfering treatment. It was published before the advent of the sulphonamides, and is a testimony of what is possible by simple medical means and late operation. In his series of 31 cases he had nine deaths, six occurring the day of admission or the following day, one on the seventh day of meningitis and one on the eighth day of general septicemia. The ninth case was the only one that did not receive early surgical treatment, and he succumbed two months and five days after admission to hospital of cardiac failure. Of the 23 that survived, six had early surgical intervention, three simple incisions of abscess, one trepanning, and two simple resections. The 17 others were treated first medically. Surgical intervention was postponed from three to 49 days, all excepting one being simple incision of abscess. One child had a resection on the ninth day following spontaneous discharge from the epiphysis. One case had no surgical intervention. His rule was to wait for the fall of the temperature before opening the abscess.

It is now well established that the sulphonamide drugs are capable of effecting a condition in the blood that will inhibit the growth of organisms. We should, therefore, test the possibilities of this drug as an aid in treatment.

It would seem rational to attempt to introduce into the blood, at the earliest possible moment, a sufficient quantity of drug to render innocuous, or impotent, organisms that are in the blood stream or in reach of body fluids. In the case of the staphylococcus particularly, which operates by means of a toxin high in necrotizing qualities and the production of thrombosis, it is urgent to administer the drug at the earliest possible moment and in quantities sufficient to the need. How great the need may be can only be determined accurately after the event, so that the assumption of the need is all that is required for the heavy administration of the drug. It is our practice to give children of about eight years of age 8-10 Gm daily. We are thus able to maintain levels of from 6 to 12 mg per cent in the blood. Larger doses may be possible, even desirable, but at this level we have had a number of reactions. The relation between the drug administered and the concentration in the blood varies greatly in different individuals. Some, when given sulphathiazole 10 Gm, will be found to have a blood level of 4 mg per cent only, while the quantities may be reversed in other cases. For instance, T. H. was given sulphathiazole 6 Gm daily for 16 days and her blood level never went higher than 3 mg per cent. She then had a reaction, and had no drug for two and one-half days. She was then given sulphadiazene 6 Gm daily, and the blood level rose to 11.9 mg per cent.

The other cases in this series reacting were as follows:

J. H., age eight and one-half. Given 8 Gm of sulphathiazole daily for one week then increased to 10 Gm daily for five days. Drug discontinued for two days because of high fever. Started on sulphadiazine 10 Gm daily for nine days, then discontinued because of high fever and rash. All drug discontinued for three weeks then restarted on sulphadiazine 6 Gm daily for three weeks, then discontinued because boy was complaining of severe abdominal pain. This stopped when drug was discontinued, and drug has not been restarted. Blood levels 4.5 to 8.5 mg per cent.

L. L., age nine. Given sulphathiazole 8 Gm for one week then discontinued because of rash. All drug discontinued for six days then restarted on sulphadiazine 5 Gm daily for six days. Rash reappeared so all drug discontinued. Blood levels 4 to 8.3 mg per cent.

E. F., age nine. Sulphathiazole 8 Gm daily for nine days then sulphadiazine 9 Gm daily for seven days then all drugs discontinued because of high fever and rash. Blood levels 2 to 13.9 mg per cent.

R. N., age ten. Sulphathiazole 8 Gm daily for 13 days then discontinued because of high fever. No drug for 24 hours then started on sulphadiazine 8 Gm daily. Was able to tolerate sulphadiazine for several months in different dosages. Blood levels 6.5 to 12.3 mg per cent.

J. LaR., age ten. Sulphathiazole 7 Gm daily for 13 days then discontinued because of high fever. Restarted on sulphadiazine which he tolerated for a long period of time in different dosages. Blood levels 3.3 to 12 mg per cent.

B. W., age eight. Sulphathiazole 6 Gm for four days, then discontinued.

for 24 hours, then restarted on sulphadiazine 8 Gm daily. Blood levels 1 to 10.1 mg per cent.

It has been proved that pathogenic organisms can become drug-resistant, and that probably also happens with staphylococcus and streptococcus.⁵ This would lead us to believe in large doses while the organism is still vulnerable. Reactions to the drug in use may make it necessary to discontinue its administration. Thus when a patient is having sulphathiazole administered shows signs of a rash, high temperature, nausea, or blood in the urine, we discontinue it for a few days and then begin again with sulphadiazine. It has been found that this may then be borne for the remainder of the period desired.

The question of initial large doses is so urgent that one is not justified in testing out the patient to estimate his ability to tolerate the drug. There is apparently no evidence available that patients who do not tolerate the drug without reaction are not benefited from its action. The sensitivity or allergy occurring in some patients from the drug cannot be foretold in all cases by skin tests, as some giving no skin reaction may react violently to the drug.⁶

There is not as much nausea caused by the drug as is commonly believed. It should be remembered that the very ill patient is often nauseated before the administration of the drug and nausea is not a valid reason for not giving the drug. The problem of the period during which the drug should be administered is primarily involved with the need, and, secondarily, with the sensitivity that develops in the patient.

The drug does not militate against the patient's ability to develop his protective substances against the toxin of the bacteria. While antitoxin has been found to have been ineffective in having any bactericidal value *per se*, yet it is known to neutralize the toxin. Sulphonamides do not inhibit the antigenic power of the toxin. While there is much less toxin produced from degenerating organisms, still what toxin there is has the power to raise the natural antitoxin against the specific infection—witness the rise in the staphylococcus titers in the cases in his series. This is an important point, as the production of immune bodies is of great value in overcoming an infection. Again the rise in the staphylococcus titer of a patient is of diagnostic value as to the recognition of the organism, since in cases that have received treatment early it is not often possible to recover the germ from either the blood or the local lesion where the latter is not opened.

The question of positive blood culture is one that is frequently discussed as being an evidence of the degree of infection present. A study of our cases does not appear to follow any such pattern. The constancy of the finding of organisms in the blood of a patient cannot be accurately foretold from his clinical condition. Experimentally, we know that a lethal dose of organisms may be introduced into the blood and in a few minutes none can be recovered and later can be recovered.⁷ Since the introduction of sulphonamides the picture of the relationship of positive or negative cultures to degree of infection is more obscure than ever. The only rational basis for study of the disease

seems to me to consist in the presence of a local lesion, roentgenologic changes being obligatory. In addition, there may be the recovery of the germ from the blood or pus, and the staphylococcus titer which indicates the specific reaction to the antigen of the toxin. When these conditions are fulfilled one has osteomyelitis.

Reports of cases treated by use of the drug with no incision of the lesion in bone, have been reported by Hoyt, *et al*.⁸ They report no deaths in the 12 cases reported. These cases were all staphylococcus. This series constitutes a unique record, and must give thoughtful surgeons reason to reassess the whole problem of the treatment of acute osteomyelitis. If cases will survive spontaneously on the one hand, and if 12 consecutive cases will survive the acute phase with medication by sulfonamides the part played by surgical incision of the local lesion is certainly not a factor in saving life.

TABLE II
OSTEOMYELITIS (JANUARY 1940—MAY 1943)
All Received Sulphonamides

Total number of cases	89
Number of cases with late incisions of abscess	64
Number with no operation	25
Number died	
Moribund on admission	3
One case incised	1
Mortality rate	4.2%

TABLE III

DEATHS

All 4 deaths were *hem. staph. aureus* cases
D. B. died 13 hrs after admission undiagnosed
D. W. died 25 hrs after admission
J. A. died 1½ hrs after admission
T. C. died 3½ weeks after admission

Our records of 89 cases, three moribund on admission, show, since sulphonamide administration, 25 not operated upon and none dead, the others operated upon and one dead, in all a mortality rate of 1.2 per cent, excluding the case moribund on admission. These results are not such that, from the mortality standpoint, incision can be altogether condemned when added to sulphonamide medication (Tables II and III).

An analysis of the case that died on the 31st day after being in hospital 24 days, is illuminating. He was ill, had positive culture and a sharp reaction. He developed an obvious superficial abscess over the upper part of the tibia. The knee contained thin pus from which staphylococcus was recovered. On the 17th day when his temperature was about 100°–100.5° F, his pulse rate 95, taking without reaction sulphathiazole 9 Gm daily, with a blood level of 8 mg %, it was decided to drain the abscess and the knee. This was done. The knee joint was opened and a soft rubber drain pushed

through the suprapatellar pouch from side-to-side. The abscess in the leg was drained. His condition the next day was much worse, temperature up, and pulse up to 120-130. He developed no new bone lesions, but he died 14 days later (Table IV). It now seems to me that the surgical interference in this case turned the scales in favor of the infection. The drainage of the knee and the abscess in the leg did not prevent the death of the boy from the spread of the disease to all the regions of his body. The result could not have been worse with no treatment of any kind. I now believe that had he had no operation he would probably have survived his acute infection. Cases that have appeared equally ill, with just such abscess and local and general symptoms, have survived when they have not been subjected to incision.

TABLE IV

Patient Thomas Cosgrove

Admitted June 12 1942	Died July 6 1942
Positive blood culture	Drainage June 22 1942
Sulphathiazole 7.5 Gm daily for 24 days	
Blood level over 6 mg %	
Titer—June 12—2 su/cc June 24—17 su/cc July 3—7 su/cc	
<i>Anatomic Diagnosis</i>	
1 Acute osteomyelitis of lt tibia (<i>hem staph aureus</i>)	
2 <i>Hem staph aureus</i> septicemia	
3 Abscesses of lungs kidneys and left chest wall	
4 Acute suppurative myocarditis	
5 Acute cardiac dilatation	
6 Early acute pericarditis	
7 Pleural effusion (bilateral)	
8 Fatty liver and acute congestion of liver	
9 Edema of gallbladder	
10 Fibrous pleural adhesions (right)	
11 Petechial hemorrhages—epicardium endocardium urinary bladder mucosa	
12 Patent foramen ovale	

In the subsidence in the acute phase a dramatic change takes place. It occurs over a period of 10-12 hours. The general reaction of the patient subsides, the intense swelling of the soft tissue at the local lesion diminishes, the underlying abscess becomes more obvious in its outline and the patient is comparatively comfortable. Later, the abscess may increase or diminish in size. When it subsides it may, in the course of three or four weeks, entirely disappear. In conditions where it becomes more superficial and enlarged it may so involve the skin that it spontaneously opens through a small opening. In our small experience, in a case where a sinus of this type is formed, there has been no large sequestrum present in the underlying bone. There are, however, small areas in the bone lined with granulation tissue and containing very small, fragile sequestra. Mostly, the cavities are subperiosteal and contain granulation tissue only. It seems that unless the abscess is too superficial it will not drain of itself and will tend to subside and behave in every particular like a tuberculous abscess. Any dead bone within it may be disposed of by the action of the tissues and their fluids or may become regenerated. It may be said that a sequestrum may be dealt with spontaneously unless a sinus develops or be made in which circum-

stance it will be necessary to remove it before the sinus will heal. The pathologic change in bone, as evidenced roentgenologically, is different to that of cases where lesions are drained. In drained lesions there is generally a wide destruction of bone together with a large involucrum, sequestration is present in over half of the cases. The first change that can be

TABLE V
CASES NOT OPERATED UPON

Hosp No	Name	Age	Day of Disease	Bone	Bact	Staph Titer	Drugs	Blood Level	Result
72 096	E C	11	7	Culcruncus	Neg	4-12 5	Sth * 8 Gm	3 9-5 9	Closed
117 812	F S	8	14	Femur	Neg	12	Sth 7 Gm	3 5-4 2	Opened upon Sin sequestrum
118 696	A A	9	21	Tibia	S A	13	Sth 8 Gm	4 3-10 2	Closed
123 232	J L	10	2	Tibia	S A	1 6-25	Sth 1 Gm Sd † 8 Gm	3 2-12	Closed
123 929	R N	10	4	Femur	S A	3-5	Sth 8 Gm	9 9-2 3	Closed
124 120	W H	6	21	Tibia	S A	4-28	Sth 8 Gm Sd 8 Cm	6 2-11 4	Closed
124 241	D S	8	14	Humerus	Neg	12 5	Sth 8 Gm Sd 8 Gm	5 5-12 5	Opened upon Sin sequestrum
124 830	G A	13	8	Femur	Neg	1-3 5	Sth 8 Gm	4-15 9	Closed
119 809	T N	5	11	Femur	Neg	4-1 2	Sth 8 Cm	3 7-7 7	Closed
120 043	F D	7	4	Femur	Neg	0 5-9 8	Sth 4 Gm	4 3-5 7	Closed
123 549	J M	10	6	Femur	S A	1 5-3	Sth 4 Gm Sd 8 Cm	4 5-11 8	Closed
124 464	J W	12	5	Cuboid	S A	2 5-12	Sth 8 Gm	8-10 2	Closed
125 463	J B	13	3	Femur	Neg		Sth 8 Gm	8 2-13 2	Closed
125 230	J F	11	6	Femur Tibia	Neg	3-6 6	Sth 8 Gm	4-8 8	Closed
122 526	B H	2	7	Tibia	Neg	1 5-5 5	Sth 8 Gm	8 2	Closed
125 451	E F	8	10	Tibia	S A	10	Sth 8 Cm Sd 8 Gm	2-13 8	Opened upon Sin sequestrum
126 302	L L	9	3	Tibia	S A	2-2 6	Sth 8 Cm Sd 6 Gm	4 8-12	Closed
126 317	J H	8	7	Tibia	S A	2-25	Sth 9 Gm	4-8 4	Opened upon Sin sequestrum
114 044	H H	3	2	Femur	Neg	1 4-4 6	Sth 5 Gm Sd 6 Cm	4-12 2	Closed
126 819	F N	8 mo	4	Tibia	Neg	2-3	Sth 8 Gm	6-14 8	Closed
126 945	T H	14 mo	7	Femur	S A	7-5 4	Sth 6 Gm Sd 6 Gm	2-11 5	Closed
126 895	K N	4	14	Femur	S A	8-5 8	Sth 5 Cm	4 2-6 4	Still in hospital
127 380	B W	8	5	Tibia	S A	1	Sth 8 Gm	1-8 4	Still in hospital
127 402	H M	9	5	Femur	S A	0 6	Sth 7 Gm	1 2-6 4	Still in hospital
115 763	M W	3	24	Lumbar vert	Neg	5 5-6 5	Sth 15 Gm	2 1-16 2	Closed

* Sth =sulphathiazole

† Sd =sulph adiazine

recognized in bone of undrained cases occurs about eight or ten days. From then on the lesion continues to lose density and involucrum very much diminished in extent sometimes hardly present may be seen. There is no obvious death of a large mass of bone except in rare cases and sequestration is present in about 10-15 per cent of cases only. Secondary lesions in other bones are rare and when they do occur, their course is very much attenuated and a nonviolent process with mild pathologic changes (Table V)

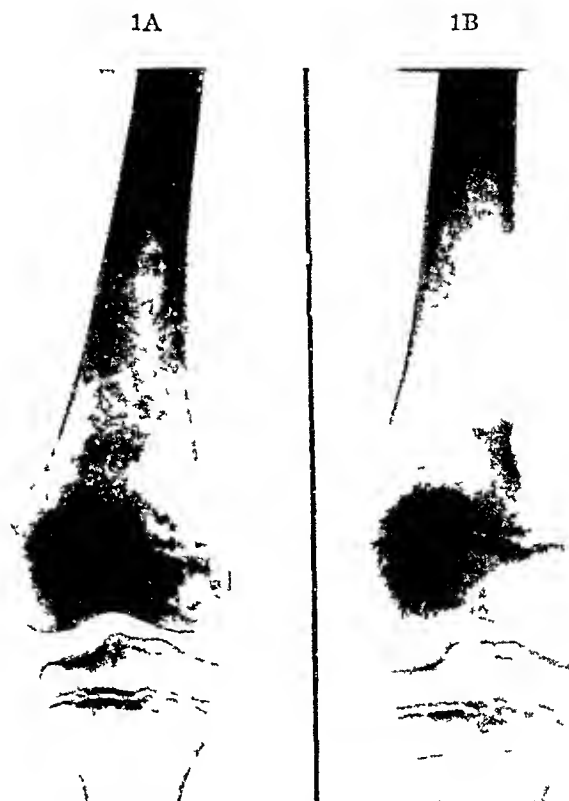


FIG 1A—T N Six and a half weeks after onset of illness Drug estimation in blood 46 mg % Titer 42 su/cc
FIG 1B—T N Fourteen months after onset of illness Epiphysis affected Pus with staphylococci aspirated from joint Diagnostic aspiration from joint

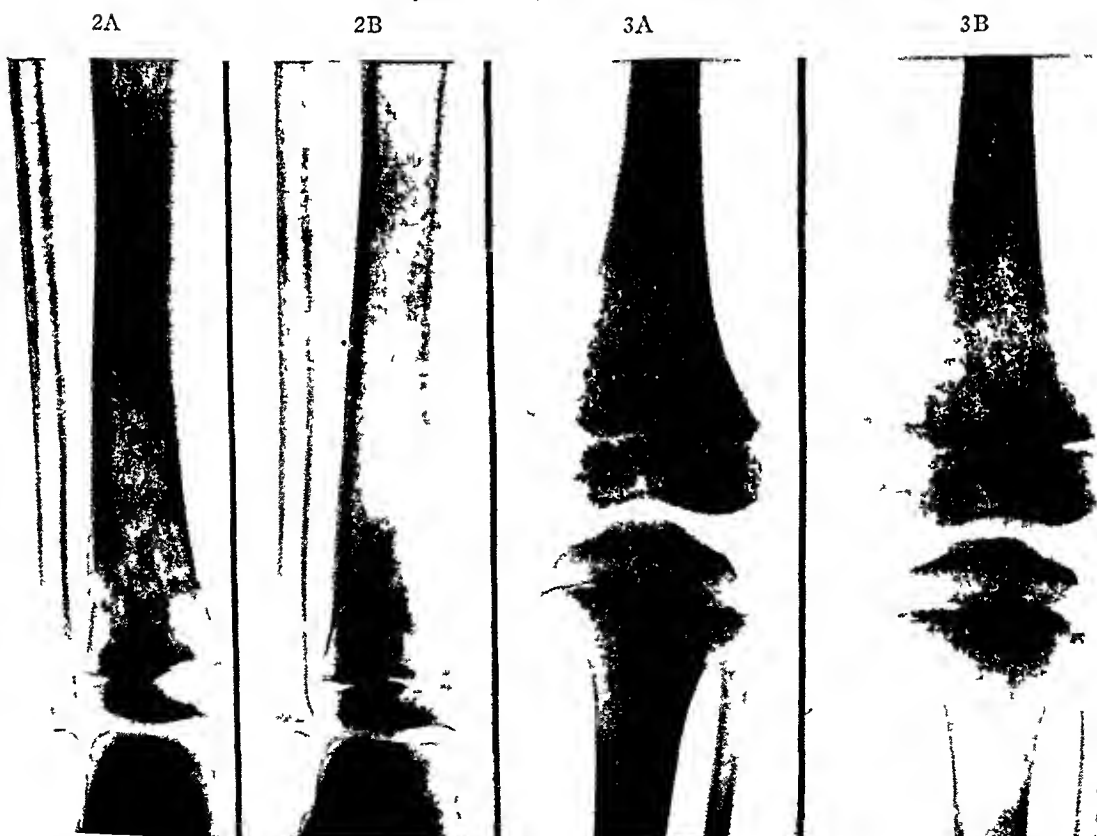


FIG 2A—W H Twenty sixth day of illness Titer 75 su/cc Drug estimation in blood 108 mg %
FIG 2B—W H Six months after onset of illness
FIG 3A—K N Two months after onset of illness Titer 95 su/cc Drug estimation in blood 146 mg %
FIG 3B—K N Four months after onset of illness Titer 166 su/cc Drug estimation in blood 83 mg %

We have had cases where contiguous joints have been involved in one instance the organism was recovered from a knee joint, where the epiphysis of the femur was involved. This case did well, and soon became afebrile, with the knee returning to normal size, and with a fair cartilage space and movement. The swelling of joints near the lesion quickly subsides and the joints recover their normal freedom of movement very quickly.

From the complete subsidence of the abscess in some cases and from its apparent nontoxic presence in others there seems to be no urgent reason for interfering with it.

The cases treated in this series have had ordinary supportive treatment together with sulfonamides. We have used sulfathiazole but it would appear that sulfadiazine is more readily borne and can be taken over a longer period of time, and a higher blood level can be maintained. It may be a better drug for the treatment of osteomyelitis. We have used no splinting except where a joint was involved, then traction was sometimes employed.

The diagnosis of the condition is to be made from first—the history. The history of a skin lesion is nearly always available when the questioning is intelligent, second, the examination of the general reaction and third, the examination of the part. No accurate localization of the lesion, as to whether it be in the epiphysis, the metaphysis or the periosteum, is necessary. This information will be available from the roentgenograms in eight to ten days. There may be also present about that time a local abscess that can be examined without pain or discomfort to the patient. The drug should be given early in the disease and in adequate amounts. When it is the disease will not be able to make much headway, and the mortality will be found only in those cases that are moribund of the infection before the true nature of the disease has been recognized and thus have not had the advantage of adequate doses of sulfonamides.

CONCLUSIONS

There is reason to believe that the administration of sulfonamides in heavy doses early in the disease may prevent deaths occurring from this disease.

An early recognition of the true character of the disease from the history, and the general and local symptoms is essential to adequate medication.

The medication must be adequate, that is large doses must be given early.

Incisional interference is not a factor in saving lives and may be a very deleterious proceeding.

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DISCUSSION—DR KELLOGG SPEED (Chicago) Doctor Robertson's title must be taken literally to assay his results and to confine our attention to acute hematogenous osteomyelitis—namely, an infection disseminated *via* the blood stream (of staphylococcus in over 80 per cent) usually from skin or soft parts, less often from the mucous surfaces of nasal passages and throat or tonsils and carried to the bones of adolescents. There may be some failures from medical treatment on account of the type of bacteria. Also, chemotherapy, even if pushed by intravenous methods to a level of 12 or 15 mg per cent, may fail in some instances to maintain sufficient bacteriostatic power to overcome the rapidity of production and pouring out of the bacteria into the blood. The earlier the drug is administered, the more powerful its control over the spread to the host's tissues and bone—ideally before any bone lesion is known to all. The percentage of occurrence of acute infectious osteomyelitis is falling off in some districts because the sulfonamides are widely employed in treatment of nasal and skin infections, acting bacteriostatically before osseous lesions may develop. After early medical treatment by massive doses we can believe that the results in a consecutive series of patients would be even better than the use of the drug plus early local and extensive operation which would interfere with the local blood supply of the bone, lower the resistance locally, and block the bacteriostatic action of the drug. My experience with this form of osteomyelitis in the bodies of the vertebrae, treated without operation, has been sad—three patients succumbing after long periods, in spite of massive dosage of the sulfa compound. However, I am limiting operation to drainage of known bone abscess and using repeated joint aspiration before open drainage.

Among the recent reports, I believe that made by Gage is most noteworthy. Any concept of the osteomyelitis must take into consideration the action of the toxins developed, especially the purely necrogenic, and that part of the toxin which increases the spread of bacteria. If the sulfonamides can paralyze bacterial growth, and thus limit or prevent the freeing of toxins, the whole chain of events, including thrombophlebitis, the number of colonies free in the blood, and ultimately the amount of bone destruction resulting, will be reduced or aborted. A late bone or subperiosteal abscess may be absorbed by leukocytes and reticulo-endothelial tissues after the action of bacteriolysins and agglutinins. Sequestra may rarely form, and an involucrum need not appear in its absence. Wilson and McKeever, in their series of 32 cases in Los Angeles, found palpatory evidence of involucrum in some, but at operation later saw only hyperplastic bone and no abscess. Together with Wilenski, they still favor operation for established osteomyelitis. Gage insists on daily administration of 60,000 to 100,000 units of potent antistaphylococcic serum until toxemia subsides. In the mild infections practically no bone change may appear as the toxins failed to kill bone, others may terminate as Brodie's abscess, with only a small local death of bone. The results also vary on the point of localization within the bone of the carried infection. If it starts as an easy spread *via* the marrow, comparable to a rapid lymphatic spread, we can look for a wider death of bone and more pus, if it starts in or near the cortex and spreads only locally under periosteum, the result may be localized abscesses pointing to the surface, relatively easy to drain.

Additional reports will probably verify Dr Robertson's results. We await also, reports on the use of penicillin, which is nontoxic and especially adapted to bacteriostatic action against the staphylococcus and all gram-positive forms of bacteria. While it has not yet proven of value in subacute bacterial endocarditis, in dosages of 30,000 to 40,000 Oxford units in 24 hours, according to Herrell, it does clear the blood stream of bacteria and may act favorably in acute infectious osteomyelitis.

DR ALBERT KEY (St Louis, Mo) I agree with Dr Robertson that the time to treat osteomyelitis with sulfonamides is before it starts, and after it starts I think one should realize that the efficiency of the sulfonamide varies inversely with the number of organisms present in a given focus, and inversely with the amount of necrotic tissue present in a given focus. It is for that reason that sulfonamides will clear the blood stream and not sterilize the focus in the bone.

I have seen a few cases of osteomyelitis that have had what the doctors who were treating them thought was the limit of sulfonamide therapy, in which the disease has progressed to the point where they got pathologic fractures. They got involvement of joints and they got widespread destruction of bone.

The question in my mind, and one which I am not yet able to decide, is: Does an incision for drainage—and by that I do not mean an extensive operation but an incision for drainage—lower the resistance locally to infection in the bone or anywhere else? Until there is some evidence to prove that, I believe that when, and if, you can diagnose the presence of an abscess in bone and your patient is in good condition, that should be drained. You should also give them sulfathiazole, all you think they can take.

The other question is: How long are you going to keep up your sulfathiazole? In my experience, these cases treated with sulfathiazole, and sulfathiazole alone, have formed sequestra after the sulfathiazole was stopped. After function of the limb was resumed they have flared-up again and have eventually required operation for drainage and removal of sequestra.

I still feel that there is a very definite place for surgery in the treatment of acute osteomyelitis, and that that place is the drainage of the abscess as soon as the patient is in condition to stand the operation. I do not believe that the drainage in the case that Doctor Robertson showed was responsible for that boy's death. He died of septicemia, and he died about 14 days after his operation.

DR D E ROBERTSON (Toronto, Ontario, closing) I do not think I have anything to add, except to say what I might have said before, that those children who do not tolerate sulfathiazole were given sulfadiazine. I think probably it is just as good a drug, and I think with sulfadiazine one can maintain a higher level than with sulfathiazole, and it is much better borne.

I want to say, in conclusion, when the child is recovering and is well of the acute phase, and can stand an operation for the drainage of abscess, just consider whether or not it is necessary to drain the abscess. The child has gotten well with an abscess. The secondary soft tissue swelling around the abscess has subsided, leaving the abscess so you can examine it and delimate it easily. It is slightly tender.

I think we make a great mistake draining these abscesses just because they are easily accessible. I think when we do attack them, we probably do something that is not in the best interests of the patient. At all events, when they are left without incision the results are excellent, much better in my opinion than those incised.

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REGIONAL ILEITIS

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IT IS THE PURPOSE OF THIS PAPER to report a series of cases of regional ileitis which, while not large, has been of such variation that it suggested the desirability of selecting those cases which might be utilized to outline a possible sequence of events from the standpoint of gross pathology. Many of the observations are largely confirmatory of the information already available in the voluminous literature on this subject. However, additional emphasis has been placed upon those aspects which appear to warrant it.

In their original article (1932) Crohn, and his associates³, reported a series of chronic inflammatory lesions which consistently involved the terminal ileum, stopping abruptly at the ileocecal valve, their observations suggested that they were dealing with a definite clinical entity. Since that time contrary-minded individuals have reported somewhat similar lesions at higher levels in the small intestine, together with occasional manifestations in the large bowel. In all our cases, with the exception of Case 5, the localization has been as Crohn originally described it. He suggested that the ileocecal valve appears to function as a barrier to extension into the cecum. While reported cases may tend to refute this, several of ours were of some interest in this connection. We were privileged to carry out exploratory operations and resection in two cases (Cases 3 and 7) in which observations at operation six and eight years previously had indicated that the process stopped abruptly at the ileocecal valve. Examination of the resected specimen and examination at operation showed no further progression of the process into the cecum. However, in Case 3 the ileocolostomy might have been a limiting factor. In any event, about 80 to 90 per cent of the lesions reported have been limited to the terminal ileum.

From the clinical standpoint, Crohn, and his associates, divided the condition into four phases. First, the earliest manifestations of abdominal discomfort which may be vague or indefinite but in other instances may very closely simulate acute appendicitis. Second, the ulcerative stage, which is characterized by varying degrees of abdominal cramps and diarrhea accompanied on occasions by some anemia and loss of weight. Third, the fibrosing or stenotic phase which is typified by cramps which may be obstructive in

origin, together with intermittent episodes of diarrhea. On many occasions a mass is palpable in the right lower quadrant, and the patient may have a considerable degree of anemia and emaciation. Fourth, the phase characterized by fistula formation, which fistula may be internal or external. The former may be established between loops of small or large bowel, particularly the sigmoid (our experience is outlined in Figure 5). External fistulae may appear in the abdominal wall or perineum.

In attempting to coordinate the preceding with a subsequent classification, the first two phases probably represent acute and subacute manifestations, while the last two are definitely chronic, however, as mentioned elsewhere in this paper, the subacute stage may be the phase of actual perforation and beginning fistula formation. It should be emphasized that the progression may extend over years, and that on occasions there may seem to be a marked disparity between the severity of the symptoms and the extensive changes revealed by operation. Furthermore, in isolated instances the stenotic phase may manifest itself without any satisfactory history suggestive of progression through the early phases.

In an effort to establish the sequence of progression, we have selected Cases 1, 2, 5 and 9 because of the distinctive gross appearance of the lesions as revealed by operation. Case 1 (Fig 1), because of the marked edema and absence of accompanying local signs of inflammation, was thought to represent the earliest manifestations and is largely a question of lymphatic block. Case 2 (Fig 2) would seem to be quite comparable with Case 1, there being, however, further superimposed signs of local inflammation, but still characterized by lymphatic block. Case 5 (Fig 3), while the most striking, is surrounded with uncertainties from the standpoint of classification. Although in this case there was involvement of the terminal ileum, there was in addition segmental involvement, one area involved was the third part of the duodenum. Involvement of the duodenum grossly appeared comparable with the findings in Case 1, *i e*, marked edema with a paucity of inflammatory findings. It is reasonable to assume that the segmental areas had a similar origin though varying markedly in gross appearance. Whether we are entirely justified in classifying this manifestation with regional ileitis may be open to question. Except for the duodenal involvement, grossly, this case is identical with several cases described by Jackman⁸ under the caption of "localized hypertrophic enteritis." The gross description and illustrations have much in common, and our information concerning the microscopic picture is drawn from this report. In any event, from the standpoint of history and microscopic findings we can definitely place it between Cases 2 and 9. Case 9 (Fig 4) is obviously of considerable chronicity and typical of the obstructive and stenotic phase.

In using the terms "acute," "subacute" and "chronic," we are employing them in a strictly clinical sense, without implications as to the microscopic findings. This would seem particularly desirable because in some instances the chronic lesions may show superimposed acute inflammation, while the

so-called subacute case probably shows the most active inflammatory lesion microscopically

If it is assumed that there is justification for utilizing the terms "acute," "subacute" and "chronic," it would seem desirable to review the available data in regard to the gross and microscopic pathology of regional ileitis. Grossly, the acute forms are characterized by their sharp demarcation, their sponge-rubber-like consistency, the marked edema which varies from white to pink, and the enlargement of mesenteric nodes of the involved segment. There is usually an accompanying accumulation of intra-abdominal fluid in the acute form. Grossly, the so-called subacute type is characterized by spongy consistency, sharp demarcation, and desquamation of the mucosa—in some instances in its entirety. The mucosa has been replaced by an hemorrhagic exudate, which, together with engorgement, is visible through the more or less normal peritoneum and which accounts for the fiery red appearance of the lesion grossly. Its appearance at operation may suggest recent strangulation or some embolic phenomenon. The bowel may be friable, and the two specimens of the subacute type reported in the literature (Jackman) were obtained incidental to perforation through handling. Hence, in all likelihood perforation and fistula formation may frequently occur spontaneously during this phase. After having passed through this reaction, it would seem that an intestine so affected must necessarily continue ultimately to the stenotic or fistula stages, there being little possibility of spontaneous subsidence. Grossly, the chronic forms are characterized by their thickening, rigidity and tumor formation either because of their altered character or because of adhesions between adjoining loops or extensive inflammatory reaction in lymph nodes or the adjacent mesentery. The mucosa is extensively involved by ulceration, varying in depth, but largely distributed along the mesenteric border of the intestine, with areas in which the lumen is markedly diminished in caliber. There is little or no accumulation of intra-abdominal fluid in the chronic form.

From the microscopic standpoint, there is nothing which is characteristic of this lesion. In view of the fact that practically all specimens obtained are of the chronic or subacute types, we have less conception of the microscopic appearance of the acute forms, particularly the edematous type. However, one might assume that, microscopically, the acute forms might reveal slight ulceration of the mucosa with marked thickening of all layers of bowel due to associated edema and with an infiltration of cellular elements dependent upon the severity of the reaction. Histologically (Jackman), the subacute condition is characterized by the absence of mucosa with substituted hemorrhagic exudate and an underlying submucosal reaction which almost borders on abscess formation. The peritoneum is relatively uninvolved, but intermediary layers reveal some degree of fibrosis indicative of previous inflammation. However, there is no demonstrable evidence of thrombosis, which is of interest in view of its gross appearance. Histologically, the chronic forms reveal ulceration of the mucosa of varying extent and depth with thickening

of walls and stenosis due to fibrosis, and with an infiltration of inflammatory cells which may vary depending upon the severity of the reaction. Giant cells may be present.

From the standpoint of etiology, rather exhaustive attempts have been made to determine some specificity, but to date there is nothing that has proved convincing. Tuberculosis has been fairly well excluded. Experimentally, Reichert and Mathes¹⁶ are said to have injected the corresponding lymphatics with a sclerosing agent and thus produced a lesion in the bowel which simulated the acute edematous lesion. In connection with the established observation that the process frequently stops abruptly at the ileocecal junction, one may refer to recent studies of the ileocecal region by Bargen, Wesson and Jackman.¹ They concluded that, mechanically, the ileocecal region functioned as a valve and that there was a marked diminution or actual interruption of the communications of the submucosal lymphatics in the region of the labia of the valve. Since, at least in the acute phase, its most striking and most obvious manifestation is in the form of lymphatic block, the preceding may explain the tendency for localization proximally.

The question of differential diagnosis in the acute phase is extremely difficult, and if exploration is carried out it is usually undertaken with a diagnosis of acute appendicitis. At the moment, we are referring to those instances in which the first symptoms have not extended back more than 36 or 72 hours. In our experience, it may present any of the variations of symptoms associated with acute appendicitis. Thus far, we have found no differential point which would justify a clinical distinction, although in some instances there is a history of a slight change in bowel habits for three to six months before the attack. On occasions, there has been more in the way of cramps than we usually associate with appendicitis, vomiting infrequent. However, we wish to emphasize that from a practical standpoint the differential diagnosis probably cannot and should not be attempted. While we are not certain, we are inclined to believe that roentgenologic studies would be of little value in the acute stages and, in general, would be contraindicated.

In our experience, roentgenologic studies in the acute cases, six to eight weeks following the establishment of the diagnosis by operation, have failed to reveal any findings that were diagnostic. To be sure, in most instances there had been a complete subsidence of symptoms postoperatively. However, this may either indicate inadequacy of roentgenologic diagnosis in the acute phase or the absence of roentgenographic findings may accompany subsidence of the lesion. The latter possibility certainly supports conservative therapy in the acute phases when encountered at operation.

In the instance referred to as subacute, roentgenography might show narrowing, however, in view of the associated friability, this might well be undesirable. Otherwise, our single case was characterized by cramps, an elevated white blood cell count, and the passage of several grossly bloody stools.

The chronic forms present much less of a problem from the diagnostic standpoint, but do require distinction from malignant growths and specific

granulomata. However, for practical reasons surgical intervention would probably prove to be the method of choice in any event. Roentgenologic studies in this type can be extremely helpful, and the so-called "string sign" in many instances is almost diagnostic. Chronic ulcerative colitis may simulate regional ileitis although the localization roentgenologically of the lesion in the colon and the presence of mucosal ulceration as revealed by sigmoidoscopic examination aid materially in making the distinction. It is of further interest that in many instances the palpable mass at least clinically, suggested a pelvic lesion, however, roentgenograms of the gastro-intestinal tract aided in making the distinction.

There is some difference of opinion in regard to the course to follow when the acute case is encountered at operation. There is little support for immediate radical resection. It is our definite impression that some of these subside completely, or at least remain subclinical, during the period of observation. In the series of six cases of Koster, Kasman and Sheinfeld,¹⁰ subsequent intervention was not required during the period of observation, and this coincides with our own experience. More recently, Smithy¹⁸ has reported a series of acute cases of regional ileitis which lends additional support to conservative therapy in such instances. However, others have reported a very high percentage of ultimate interventions in acute cases. When the cecum is uninvolved (100 per cent in our series), we have routinely carried out appendectomy, not with the idea that appendectomy contributed therapeutically, but because it is reassuring to have removed the appendix should there be a chronic complaint in the right lower quadrant. If a radical procedure seems indicated subsequently, it can frequently be carried out more advantageously at a second operation.

Mixter^{12, 13} has condemned the practice of appendectomy in the acute cases because of the danger of fistula formation. However, in the early manifestations, in the presence of an uninvolved cecum, there should be little danger of fistula formation as a result of the appendectomy. In any event, as Crohn, and his associates, have indicated the fistulae frequently have their origin from the ileum rather than from the appendiceal stump. Hence, they may develop incidental to the exploration rather than as a result of the appendectomy.

Insofar as the chronic stenosing types are concerned there is general agreement that short-circuiting anastomotic procedures or resection should be carried out, with the latter procedure in considerable favor, although Ginzburg and Garlock⁵ have recently presented excellent evidence in favor of ileocolostomy, with exclusion. In the majority of instances great benefit follows the aforementioned procedures although it is not uncommon for those patients who secure a satisfactory result to have two to three soft stools a day. Recurrences of symptoms are quoted in the neighborhood of 10 to 15 per cent while Cutler⁴ mentions a much higher figure and is pessimistic as to the benefits of surgical intervention. However in view of the occasional segmental involvement recurrences might well be anticipated.

Our experience with the chronic stenotic phases has been limited to seven cases, all except one of which have been treated by primary resection of the terminal ileum and cecum, with lateral anastomosis between the ileum and ascending colon. In a single instance an ileocolostomy had been carried out elsewhere two years previously, and we performed resection of the isolated loop. The foregoing procedures have been effected without mortality, and in five of the seven cases the results are quite satisfactory to date. Of the unsatisfactory, one was considered quite satisfactory for a period of four years, after which time a severe macrocytic anemia and a marked rectal stricture, of undetermined origin, developed. The remaining patient (with initial ileocolostomy), although maintaining her nutrition, continued to complain of cramps and diarrhea, and was considered to have an unsatisfactory result.

We have attempted to arrange the more characteristic examples of our cases in the sequence in which we believe the condition progresses, recognizing the hazard of doing so with a no more reliable basis than their gross appearance. We have further classified them as acute, subacute and chronic. It would seem that there is adequate support for conservative therapy in the acute manifestation. The subacute stage, because of its friability and tendency to perforation, might well require resection. We believe the chronic stenotic phase to be definitely amenable to surgical treatment, with primary resection as the procedure of election in our cases.

CASE REPORTS

Case 1—J L, white, male, age 21, was admitted to Lakeside Hospital, April 14, 1933, with a history of abdominal cramps of three to four days' duration, the pain had ultimately tended to localize in the right lower quadrant. There had been several liquid stools at the onset but subsequently the bowel movements were normal. There had been no vomiting. There was no history of previous similar difficulty. The patient was very muscular and well nourished. There was some tenderness in the right lower quadrant with marked rebound tenderness, but little, if any, spasm. Rectal examination was essentially negative. Temperature 38.5° C, pulse 90, white blood cell count 7,000, uranalysis negative.

The patient was observed for six hours, after which time an exploratory operation was carried out, through a McBurney incision. Some fluid was encountered. The terminal 12 to 14 inches of ileum was found to be markedly thickened and edematous, it was a white edema, and there was no injection (Fig 1). The nodes of the involved segment were enlarged. The process stopped abruptly at the ileocecal valve. The cecum and appendix were not involved. No other abnormalities were noted. Appendicectomy was performed. The wound was closed without drainage. No pathologic diagnosis was made. Convalescence was uneventful. Stool cultures and agglutination tests were negative for *B typhosus* para A and B. During the subsequent year the patient had no further trouble, after that we were unable to follow him. *Diagnosis* Regional ileitis (acute).

Case 2—H K, white, female, age 31, began experiencing generalized abdominal cramps about 24 hours before admission to Lakeside Hospital, April 30, 1937. The discomfort subsequently localized in the right lower quadrant. There was some nausea but no vomiting or diarrhea. She had had some slight abdominal discomfort two weeks previously, but otherwise no similar previous difficulty, although for the preceding six months she had had several soft movements daily, when previously there



FIG 1—Case 1 Color drawing of operative findings Primarily lymphatic block, characterized by edema and peritoneal fluid but with no other signs of inflammation Classified as acute regional ileitis upon basis of history and findings



FIG 2—Case 2 Color drawing of operative findings Lymphatic block not so obvious but inflammatory reaction extreme Little fluid, but segmental, inflammatory involvement of ileum striking, suggesting recent embolic phenomena or strangulation, contrasted with edematous manifestations in duodenum comparable to Figure 1 Classified as subacute and acute regional ileitis upon basis of history and associated duodenal manifestation of an obviously acute nature Only case in series with grossly bloody stools although there is a history of gross hemorrhage in Case 7



FIG 3—Case 5 Color drawing of operative findings Lymphatic block with superimposed signs of moderate inflammation characterized by edema peritoneal fluid, and redness Classified as acute regional ileitis upon basis of history and additional signs of early inflammation



FIG 4—Case 6 Color drawing of resected specimen Little evidence of lymphatic block, lesion of obvious chronicity with fibrotic changes constituting a definite tumor

had been but one. A questionable diagnosis of gastric ulcer had been made nine years before.

Examination revealed a well-nourished individual, not appearing acutely ill. There was definite tenderness in the right lower quadrant but no spasm. Rectal and vaginal examinations were essentially negative. Temperature 37° C, white blood cell count 9,000 to 13,000, urine essentially negative. The patient was observed for four hours, and it was then deemed advisable to rule out appendicitis.

The patient was operated upon through a McBurney incision. A large amount of free fluid was encountered. The terminal ileum for a distance of 14 inches from the ileocecal valve was thickened, edematous and of a reddish-pink color (Fig 2). The nodes in the corresponding segment of the mesentery were enlarged. The process stopped abruptly and did not extend beyond the ileocecal valve. The cecum and appendix were not involved. Appendectomy was performed. No pathologic diagnosis was made.

The hospital course was uneventful. The patient had roentgenograms of the gastrointestinal tract, July 29, 1937, April 27, 1940 and September 9, 1941, with essentially identical findings, *viz*, hypermotility and hyperperistalsis of small intestines, without deformity in terminal ileum or elsewhere. The patient's general health to date has been excellent, with no noteworthy abdominal symptoms. *Diagnosis* Regional ileitis (acute).

Case 3 —L W, white, female, age 26, was admitted to Lakeside Hospital, August 6, 1935, with the complaint of abdominal cramps and diarrhea. The patient apparently had been in good health until seven years before, at which time she began having cramps and diarrhea. Five years before admission she was admitted to another hospital, observed and operated upon for anal abscess and fissure. One year later she returned to the same institution and an abdominal exploration was carried out. A bilateral salpingectomy, left oophorectomy and appendectomy were performed. Further exploration revealed a regional ileitis involving the terminal 18 inches and stopping abruptly at the ileocecal valve. A lateral anastomosis was performed about the lesion. The patient experienced marked benefit for a period of two years, when a recurrence of symptoms occurred which continued to time of admission to this hospital.

There had been some recent loss of weight and stools five to ten times a day, but no pus or blood were noted. The patient was well nourished. The general physical examination was negative save for some tenderness in the right lower quadrant. Laboratory data were negative except for hemoglobin of 60 per cent, and red blood cell count of 3,700,000. A barium enema revealed a functioning anastomosis, and findings in the terminal ileum suggestive of ileitis. In view of recurrence of symptoms, exploration was thought justifiable. Many adhesions were encountered, and a process was found in the terminal ileum characterized by thickening and edema, stopping abruptly at the ileocecal valve and extending up to about eight inches from the anastomosis. There was no fluid. Exploration of the remaining small and large intestine showed no involvement. Without disturbing the anastomosis, the short-circuited intestine (60 cm) was resected to include a small portion of cecum. Grossly, the resected portion was comparable with findings in chronic regional ileitis, and the histologic examination was consistent with that diagnosis. The lesion did not extend beyond the ileocecal valve.

The postoperative course was uneventful. The patient was readmitted to the hospital one year later, with the history that, while there had been temporary benefit following operation, at the time of admission there was a recurrence of cramps and diarrhea. However, there had been no loss of weight and the previous moderate anemia had disappeared. *Diagnosis* Regional ileitis (chronic). *Result* unsatisfactory. Recently readmitted for further resection.

Case 4 —J W, white, male, age 30, was admitted to Lakeside Hospital, March 15, 1937, with a complaint of abdominal cramps and loose bowel movements of two

or three days' duration. Although discomfort was rather diffuse, there was a tendency to localization to the right of the umbilicus. There had been no nausea or vomiting. There was a history of episodes of diarrhea of very brief duration for several years, but at no time had there been cramps of the present severity.

The patient was a well-nourished, almost obese male. Examination of the abdomen revealed rather diffuse tenderness, most marked to the right of the umbilicus. There was no spasticity. There was definite rebound tenderness. Temperature 38°C , white blood cell count 16,000, urine essentially negative. The patient was observed for 12 hours, during which time discomfort increased and there was some further localization in the right lower quadrant. Prior to operation the temperature was 38.2°C , white blood cell count 24,000.

Exploration was carried out through a McBurney incision, with a diagnosis of questionable acute appendicitis. Considerable fluid was encountered. The terminal ileum, for a distance of 16 inches, was quite red, thickened and edematous. The process terminated abruptly at each end and stopped abruptly at the ileocecal valve. There were enlarged nodes in the segment of mesentery of the involved bowel. The cecum and appendix were not involved. An appendectomy was performed. No pathologic diagnosis was made.

The subsequent hospital course was uneventful. Roentgenograms of the gastrointestinal tract, September 8, 1937, revealed no abnormalities. The patient has had no further trouble to date. *Diagnosis* Regional ileitis (acute).

Case 5—F S, white, male, aged 27, was admitted to Lakeside Hospital, April 2, 1934, with a history of having been in good health until five days before admission. At this time he experienced abdominal pain, more marked in the left lower quadrant than the right, and accompanied by nausea and vomiting. There had been obstipation but the patient had passed flatus. An appendectomy had been performed through a right rectus incision four years before, and a few months thereafter a bilateral inguinal herniorrhaphy.

Examination showed a slightly undernourished and pallid appearing individual not acutely ill. The abdomen was possibly slightly distended but there was no visible peristalsis. There was some tenderness in the left lower quadrant but no spasm. There were scars of a right rectus incision and of bilateral inguinal herniorrhaphy. Temperature 37.8°C , white blood cell count 21,000, urine essentially negative. Our impression was partial intestinal obstruction. A barium enema revealed no abnormalities, and because of persistence of vomiting in the absence of distention, we suspected a high obstruction. A small amount of barium by mouth revealed partial obstruction in the region of the second and third part of the duodenum. The patient was observed for nine days, after which time he passed several grossly bloody stools.

Exploration was immediately carried out, with a diagnosis of partial intestinal obstruction. The right rectus scar was excised and the peritoneal cavity was entered. A small amount of slightly cloudy fluid was encountered. After freeing many adhesions, we encountered two striking areas of segmental involvement of ileum measuring 12 to 18 inches in extent, one of which extended up to and stopped abruptly at the ileocecal valve (Fig 3). The bowel over the involved area was a fiery red color with no extension of the process into the mesentery. There was some segmental thickening and enlargement of nodes in the mesentery. Our first impression was that it was some embolic phenomenon or a recently released volvulus, but the condition of the mesentery ruled this out. Exposure of the third part of the duodenum (indicated in the roentgenogram) revealed marked edema involving the peritoneum and that portion of the duodenum observed. It was a white edema and in marked contrast to the process at previously described levels. In view of the extent of the process, resection was not contemplated.

The postoperative course was quite uneventful save for a continuance of bloody diarrhea for several days and a moderate parotitis. The patient was followed for about two and one-half months after operation, during which time he gained considerable weight and was entirely free of the symptoms which brought him to the hospital. We were unable to follow him after this time. *Diagnosis* Regional ileitis (subacute)

Case 6—M T, white, female, age 34, was first admitted to Lakeside Hospital, July 1, 1935, with a history of diarrhea (5 to 15 stools daily) and vague abdominal discomfort of some four years' duration. There had been an accompanying loss of weight. Following investigation, her condition was diagnosed as enterocolitis of undetermined origin, although in view of many sensitivities it was considered as possibly allergic in origin. The patient was apparently somewhat improved until six months before the present admission, at which time there was an exacerbation of symptoms, *i e*, diarrhea (4 to 8 stools daily) and cramps of increasing severity.

At the admission on September 13, 1937, the patient was moderately well-nourished, and did not appear acutely ill. The general physical examination was essentially negative save for lower abdominal tenderness in both quadrants, more marked on the right where there was a definite, tender palpable mass. Barium enema revealed a typical "string sign" of the terminal ileum. This was confirmed by roentgenograms of the gastro-intestinal tract. Hemoglobin 78 per cent, white blood cell count 8,000, red blood cell count 4,200,000, urinalysis essentially negative. Stools No entameba, benzidine 2-3 ++++. In view of the progressive symptoms and obvious early obstruction, resection was deemed advisable.

At operation, the terminal two and one-half feet of ileum presented the typical picture of chronic ileitis, with the process stopping abruptly at the ileocecal valve. The cecum and appendix were not involved grossly. The involved portion of the ileum and part of the cecum were resected, and a lateral ileocolostomy was carried out. Microscopically, the lesion was consistent with the usual picture of chronic regional ileitis. The process stopped at the ileocecal valve, although there was some slight involvement of the cecum, but merely what one might anticipate of tissues in juxtaposition to such a process.

The postoperative course was uneventful. Following discharge from the hospital the patient did exceedingly well, gained weight and was quite comfortable. She had two or three soft formed stools a day. *Diagnosis* Regional ileitis (chronic)

About July 17, 1941, the patient complained of dizziness, weakness, shortness of breath and pain upon defecation. Investigation revealed an hemoglobin of 35 per cent, red blood cell count of 1,400,000, and white blood cell count of 3,350. Proctoscopic examination revealed a stricture about two inches from the anus. Biopsy of this was negative. Several Frei tests were inconclusive. *Diagnosis* Macrocytic anemia due to deficient absorption, stricture of rectum of undetermined origin. Result unsatisfactory.

Case 7—A K, white, female, age 40, was admitted to Lakeside Hospital, July 29, 1936, with a history of abdominal discomfort for some ten years. At onset, ten years previously, an appendectomy was carried out at another hospital, which procedure was followed by a fistula. Some time thereafter the fistulous tract was excised, and it was found to communicate with a lesion in the terminal ileum, which was described as typically tuberculous, although there was no histologic confirmation. Some type of resection was carried out. The patient did fairly well until three or four years before the admission to Lakeside Hospital, at which time she experienced abdominal cramps, diarrhea and loss of weight. Two years before admission she had had a severe hemorrhage. The aforementioned symptoms persisted, and the patient followed a downhill course until the admission to Lakeside Hospital.

The patient was quite emaciated and obviously chronically ill. General examination was negative save for abdominal findings. There was a small hernia in the supra-

pubic scar, but no mass was palpable. However, on pelvic examination there was a definite mass filling the pelvis which was difficult to separate from the uterus. Hemoglobin 35 per cent, red blood cell count 2,000,000, white blood cell count 4,000. Roentgenograms revealed deformity of the terminal ileum, and suggested that the mass in the pelvis represented the terminal ileum. Although the patient was a bad risk, exploration was thought advisable.

At operation, the mass in the pelvis was delivered readily and was found to consist of a mass of agglutinated small bowel, apparently centering about the terminal ileum. There was one loop of jejunum so intimately involved that resection and end-to-end anastomosis were carried out (Fig 5A). Following this it was feasible to resect the terminal 45 cm of ileum and the cecum, a lateral ileocolostomy being carried out.

The patient's course was stormy for several days after operation but uneventful thereafter. She was completely relieved of all symptoms, and gained 45 pounds in the first year. The patient continues to have two to three soft movements a day, but they are not accompanied by discomfort. She remains well to the present time.

Diagnosis Regional ileitis (chronic)

Case 8—M L H, white, female, age six years, was admitted to Glenville Hospital in September, 1936, with a history of periumbilical and right lower quadrant cramps of 48 hours' duration. There was no history of any similar previous difficulty. Bowel movements had been regular.

Examination revealed a moderately well-nourished white female, who did not appear seriously ill. There was some tenderness in the right lower quadrant but neither rigidity nor distention. Temperature 38° C, white blood cell count 11,000, urine negative. In view of the persisting cramps it was deemed advisable to carry out an exploratory operation, with a diagnosis of acute appendicitis or some type of partial obstruction.

Under gas-oxygen-ether anesthesia, a short right rectus incision was made. The peritoneal cavity contained considerable clear fluid, the appendix was normal. However, the terminal five inches of ileum was markedly edematous and of a pinkish color, nodes in the involved segment were definitely enlarged, the cecum was not involved. Appendectomy was performed. No pathologic diagnosis was made.

The subsequent hospital course was uneventful. Insofar as can be ascertained the child has had no further trouble.

Diagnosis Regional ileitis (acute)

Case 9—S B, a white, female, age 20, was admitted to Lakeside Hospital, December 28, 1937. Four years previously she had been admitted to the hospital with a history of vague abdominal complaint of some four days' duration, localizing in the right lower quadrant, unaccompanied by nausea or vomiting. An appendectomy was performed, without abdominal exploration. The histologic report was chronic appendicitis. Following this, the patient continued to have episodes of abdominal cramps accompanied by distention. In general, the discomfort increased in severity and was, on occasion, accompanied by fever and gradual loss of weight. More recently, there had been some relation to the menses, particularly the last, which began some ten days previously, and was accompanied by fever and the finding of a mass in the right lower quadrant, which was thought to have its origin in the pelvis.

The patient was operated upon on the Gynecological Service, with the diagnosis of possible ovarian cyst.

At operation, the mass was found to have its origin in the terminal 12 inches of the ileum, with extensive involvement of nodes in the corresponding segment of the mesentery. The lesion was obviously chronic and the site of fibrous changes (Fig 4). There was no fluid. The ileum and a portion of the cecum were resected and a lateral ileocolostomy was carried out.

Histologic Report Pathologic findings consistent with chronic regional ileitis

The postoperative course was uneventful for the first week. On the tenth postoperative day the patient was operated upon again because of intestinal obstruction. An adhesion to the midline scar had produced complete obstruction of the small intestine at a level about four feet above the anastomosis. The subsequent course was uneventful. Since that time, the patient has gained considerable weight and, in general, is quite comfortable. She does have from one to three soft stools per day, when under nervous strain this may border upon diarrhea. *Diagnosis* Regional ileitis (chronic)

Case 10—W. H., white, male, age eight, was admitted to Lakeside Hospital, August 2, 1938. Three days before admission he began having abdominal discomfort, more marked on the right side than on the left. There had been no nausea, vomiting or diarrhea. There had been some abdominal discomfort one year previous to admission.

Examination revealed a moderately well-nourished boy, who did not appear acutely ill. There was some tenderness in the right lower quadrant but no spasm. Temperature 38° C, white blood cell count 8,600, urine negative. The diagnosis was indefinite, but after 18 hours' observation there was no change in the findings and exploration was carried out through a McBurney incision. (The patient's family had had a recent unfortunate experience with peritonitis from a ruptured appendix.)

At operation a moderate amount of fluid was encountered. The terminal three inches of ileum was thickened and edematous, but only slightly injected. A number of enlarged nodes were palpated in the mesentery. The process stopped abruptly at the ileocecal valve. The cecum and appendix were not involved. The latter was removed. There was no pathologic diagnosis.

The postoperative course was uneventful. The patient had roentgenograms of the gastro-intestinal tract, April 29, 1939, with no unusual findings. His general condition to date has been excellent, with no recurrence of symptoms. *Diagnosis* Regional ileitis (acute)

Case 11—L. D., white, female, age 30, was admitted to Lakeside Hospital, March 2, 1939. She had apparently been in excellent health until six months before admission, when she began experiencing vague abdominal discomfort characterized by a feeling of distention, there had been no diarrhea. For the preceding eight weeks there had been a continuance of the foregoing symptoms with the addition of night sweats and intermittent elevation of temperature. About ten days before admission there had been a severe episode of abdominal pain, which localized in the right lower quadrant, with accompanying nausea and vomiting. Upon admission to the hospital the patient appeared chronically ill.

General examination revealed no abnormalities. Examination of the abdomen revealed a firm, somewhat tender mass in the right lower quadrant, measuring 8 x 6 x 6 cm. It was slightly movable and could be readily palpated on vaginal examination. Temperature 39° C, hemoglobin 80 per cent, red blood cell count 4,300,000, white blood cell count 23,000, urine essentially negative. In view of the history, an appendiceal abscess was considered, but the impression rather favored regional ileitis. The temperature subsided in two weeks and a barium enema revealed a "string sign." A diagnosis of chronic regional ileitis was made. The patient was readmitted several weeks later for operation. Signs of inflammation were entirely absent otherwise the findings were the same.

At operation an inflammatory mass was found in the right lower quadrant, consisting primarily of thickened and fibrosed terminal ileum but further contributed to by adhesion of an adjacent loop of small bowel, omentum and the transverse colon (Fig 5 B). There was no fluid. The terminal ileum and a portion of the cecum were resected, and an ileocolostomy was carried out. Grossly, the cecum was not involved, however, the ileocecal valve projected into the cecum in a cervix-like fashion. Microscopically,

there were the usual findings in the ileum with only the degree of reaction in the cecum that would occur in any stricture in juxtaposition. The postoperative course was uneventful. There was some diarrhea for several weeks following discharge. At the present time the patient's condition is excellent. She has gained weight. She does have two or three soft movements per day. *Diagnosis* Regional ileitis (chronic)

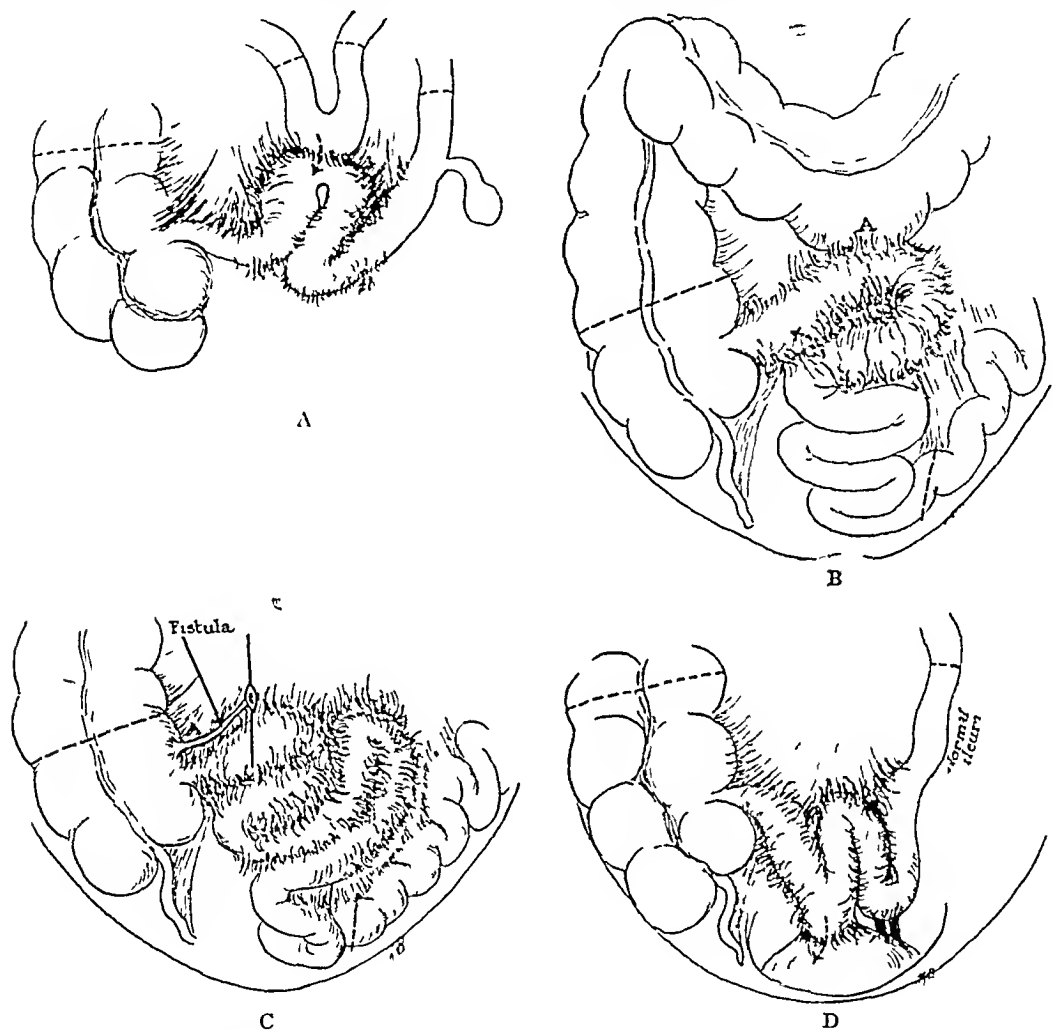


FIG 5—Examples of potential and actual internal and external fistulae (A) Case 7 Between loops of ileum and jejunum (B) Case 11 Potential at (A), minute communications at arrow (C) Case 12 Between cecum and exterior, following biopsy (D) Case 13 Between ileum and bladder at arrow

Case 12—Y F, white, female, age 32, was admitted to Lakeside Hospital, October 1, 1941, with a history that 11 months previously she had experienced cramps and a feeling of distention. This continued for five months, when a mass was noted in the right lower quadrant and pelvis. By this time there was some loss of weight and a moderate degree of anemia. The mass was considered an ovarian cyst by her attending physician and exploration was carried out. An inflammatory mass was found, consisting of terminal ileum and a portion of cecum, and a biopsy was taken from the latter. Following operation a sinus appeared in the wound. The patient continued to have abdominal discomfort until the time of admission to Lakeside Hospital. The patient was moderately well-nourished. There was a sinus tract in the midline scar. There was a palpable mass in the right lower quadrant which was slightly tender and could be palpated on bimanual (vaginal) examination. Barium by rectum and

mouth revealed a lesion which apparently involved not only the terminal ileum but also a portion of the cecum. Laboratory data were essentially negative. There was no anemia at this time. A diagnosis of chronic regional enteritis was made.

The patient was operated upon through a right rectus incision, and the fistulous tract was found to extend to the cecum (Fig 5C). The terminal 16 inches presented a typical appearance of chronic ileitis, although, for the first time in our series, the process definitely extended beyond the ileocecal valve. The terminal ileum and cecum were resected, with lateral ileocolostomy. Grossly, the specimen showed involvement of a portion of the cecum. Histologic findings were consistent with chronic ileitis and confirmed the involvement of the cecum.

The subsequent course was uneventful. The patient has gained weight, is in excellent health, and has no complaints. *Diagnosis* Regional ileitis (chronic).

Case 13—J. K., white, female, age 40, was first admitted to another hospital about 18 months prior to admission to Lakeside Hospital. She complained of lower abdominal discomfort and burning upon urination of several weeks' duration. Operation shortly after admission to the other hospital is said to have revealed extensive inflammation in the pelvis, the abdomen having been closed following exploration. Following the operation urinary symptoms became exacerbated, and some time thereafter the patient noted passage of brown, semisolid material per urethra. At the time of admission to Lakeside Hospital (on the Genitourinary Service), October 13, 1941, the patient had sustained a loss of 20 pounds in weight. It was thought that the patient had an enterovesical fistula. Cystograms were normal, but cystoscopy revealed an inflammatory process involving the posterior wall of the bladder. No fistula was demonstrable. Pelvic examination showed a mass in the right vault extending into the right lower quadrant. A barium meal revealed contrast medium passing into the bladder apparently from the region of the terminal ileum. Thus, an enterovesical fistula was demonstrated, which was thought to be associated with a chronic regional enteritis.

Operation revealed an inflammatory mass in the right lower quadrant consisting of agglutinated folds of the terminal ileum, one of which was firmly adherent to the posterior surface of the bladder (Fig 5 D). There was no fluid. The bladder was thickened in a manner comparable to the adjacent bowel. The bowel was freed from the bladder and the opening in the bladder was closed. The terminal two and one-half feet of the ileum and the cecum were resected, and a lateral ileocolostomy was done. Grossly, the specimen was typical of chronic ileitis, the process stopping abruptly at the ileocecal valve. Histologic report was consistent with the diagnosis of regional ileitis.

The patient was kept on catheter drainage for one week. The postoperative course was uneventful. The patient has gained considerable weight, has no bladder symptoms, and is progressing satisfactorily to date. *Diagnosis* Regional ileitis (chronic).

The author wishes to express his appreciation of the assistance given by Dr. Eugene Freedman, of the Department of Roentgenology, and by the Staff of the Institute of Pathology of Western Reserve University. Especial appreciation is due Miss Theodora Bergsland, the artist.

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METASTASIZING INTRACRANIAL TUMORS

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THE OCCURRENCE OF METASTASIS from any primary intracranial neoplasm has been the subject of great interest to both clinicians and pathologists for many decades. Particularly has this been true when metastasis seemed to have occurred outside the central nervous system and its envelopes. To be sure, there have been a number of reports of such metastasis, but considering the many thousands of intracranial tumors that have been studied in many large clinics, these few reports speak well for the rarity of such a metastasizing lesion. In view of this, we wish to report one case in which an intracranial tumor appears to have metastasized to the lungs and hilus nodes.

Case Report—A male, age 32, registered at the Mayo Clinic, May 20, 1938, because of headaches and vomiting. In January, 1936, he first had noticed a lump in his forehead, very slightly to the left of the midline. He had persuaded his family physician to lance this, but only blood had been obtained. During the next two months the swelling had pulsed and about this time he had found that he could push the lump back into his head, although this had been somewhat painful. In April, 1936, he had been examined elsewhere, and roentgenotherapy had been employed. This had given relief from headaches for about two weeks, they then gradually had returned. In August, 1936, he had received another course of deep roentgenotherapy, with similar results, however, he had been able to get along fairly well until September, 1937, when the headaches had become so severe that he had requested, and had received, another course of treatment. In February and March, 1938, his headaches again had become severe, and at this time they had been associated with frequent vomiting.

When he was first examined at the clinic, neurologic and general physical examinations disclosed the presence of a small mass in the forehead, with obvious erosion of the frontal bone. The optic disks were choked four diopters, about equally in both eyes. The roentgenograms of the skull confirmed the clinical impression of erosion of the frontal bone and, in addition, there was evidence of prolonged increased intracranial pressure.

On May 28, 1938, one of us (J G L) removed a large right parasagittal frontal tumor, which had completely surrounded and invaded the longitudinal sinus. It was necessary to resect the sinus to the entrance of the Rolandic veins and to remove a part of the invaded and eroded frontal bone. The tumor weighed 140 Gm., and measured 8 x 7 x 6 cm (Fig 1). The patient made an uneventful recovery, and when he was dismissed, July 18, 1938, the wound had healed.

He returned to the clinic in November, 1938, because of the presence of a pedunculated growth, two centimeters in diameter in the anterior end of the operative incision. Radium was applied to this at that time and again in February, 1939, because of recurrence. In spite of this, the patient was able to work from August, 1938, to June, 1939, when headaches again began to be severe. In July, he had a generalized

convulsion, followed five days later by numbness associated with paralysis in the left half of his face. He again returned to the clinic, August 1, 1939, because of the persistence of the facial weakness and of dysarthria. On August 3, 1939, with the use of local anesthesia, a tumor the size of a hen's egg (40 Gm) was removed from the original site of the neoplasm. He did only fairly well after this procedure and, September 1, 1939, a plastic closure of a cerebrospinal fistula, which had developed soon after the second operation, was performed. He had a very stormy course after this operation, and died, in hyperthermia, September 11, 1939, approximately three years and nine months after he first had noticed the lump in his forehead. A complete necropsy disclosed the defect of the recent removal of the frontal tumor and, in addition, another large residual and recurrent tumor in the right frontotemporal lobes (Fig 2). There also was evidence of terminal endovinitis and mild meningitis.

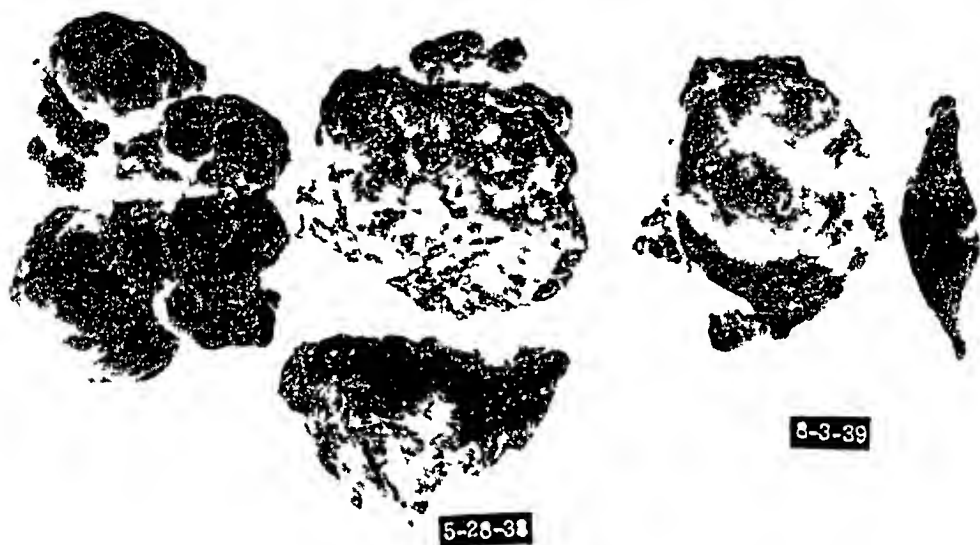


FIG 1.—Tumors removed at the two operations

Gross examination disclosed nodules of firm gray tissue scattered throughout all lobes of both lungs (Figs 3 and 4). The hilus nodes also appeared to be infiltrated by small tumor masses. These nodules varied in size up to four millimeters in diameter. There was also pulmonary infarction from arterial emboli.

Histologic examination of the brain tumor disclosed a malignant hemangioblastoma (Grade 3), and all three specimens (two operative and one postmortem) were found to be identical (Figs 5, 6 and 7). Sections of the milary nodules in the lungs and hilus nodes disclosed a tumor of identical structure (Fig 8) to that found in the brain. There was no doubt as to the identity of the tumor.

Sections of the removed tumors and of the residual tumors were examined. The following stains were used: Hematoxylin and eosin, Mallory's phosphotungstic acid stain, Perdrau's silver stain, Cajal's and Hortega's stains, and cresyl violet. The hematoxylin and eosin stain disclosed a tumor made up of small blood vessels, capillaries, sheets, strands and islands of endothelial-like cells. Thin-walled vascular channels lined with endothelial cells frequently were found filled with fat, oval and occasionally somewhat spindle-shaped, hyperchromatic and foam-like endothelial cells. The nuclei were usually small and the cytoplasm was misty and even foam-like. Mitoses were everywhere abundant and were typically present in the intima of the small proliferating blood vessels (pseudocapillaries). The larger vessels occasionally contained erythrocytes, but many did not.

The tiny tumor nodules found in the lungs, pleura and hilus nodes were discrete, circumscribed masses of cells, with exactly the same characteristics as seen in the intracranial tumor. Examination of sections of the metastatic tumors that had been stained with *Perdraus silver* stain revealed the typical vascular reticulin pattern of a hemangioblastoma (Fig 9) just as it did in the case of sections of the intracranial tumor obtained at operation and at necropsy. Malloiy's phosphotungstic acid stain,

FIG 2



FIG 3

FIG 2—Recurrent hemangioblastoma in coronal section at the level of the optic chiasm

FIG 3—Metastatic tumors in the lung (arrows) from primary intracranial hemangioblastoma

Cajal's stain and Hortega's stain were only of minor additional value in proving that the tumor was not of glial origin but definitely of vascular origin

COMMENT

The problem of metastasis encountered any place in the body is not always easily solved, mainly because it is not always possible to be sure which neoplasm is the primary one. This is particularly the situation when one is dealing with metastasis of intracranial tumors. As was, facetiously but correctly, remarked by one pathologist "The tumor cells do not oblige us with arrows on them showing which way they are going"—certainly one wishes they did

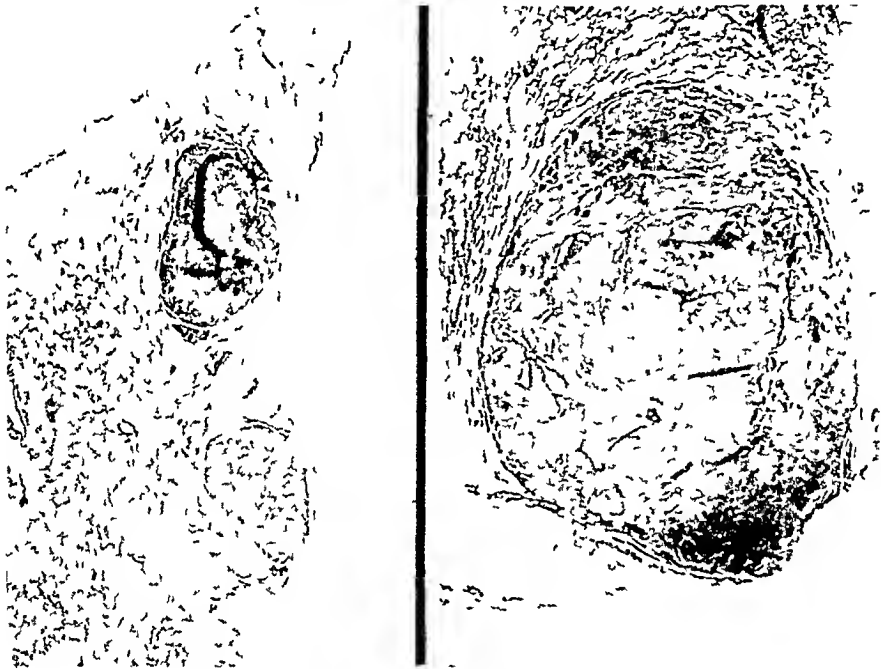
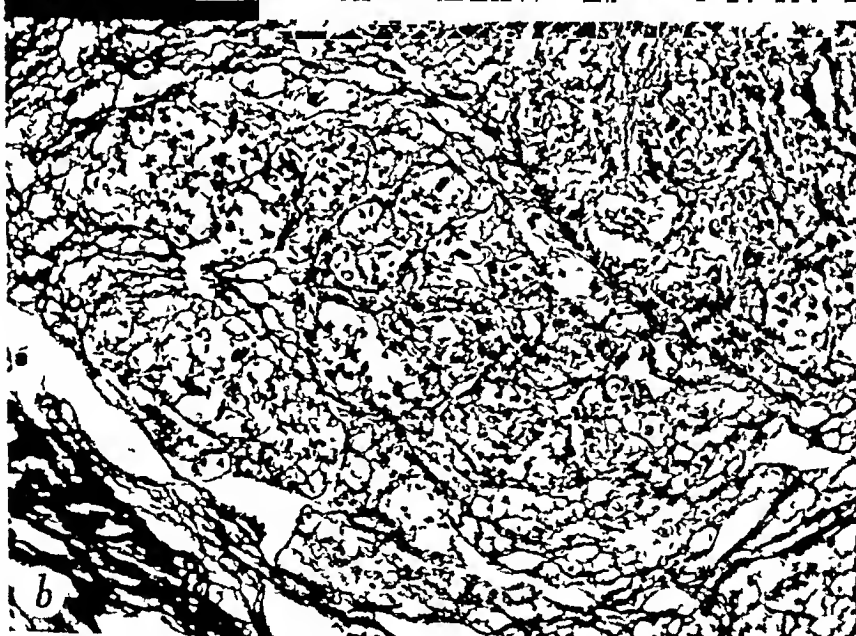
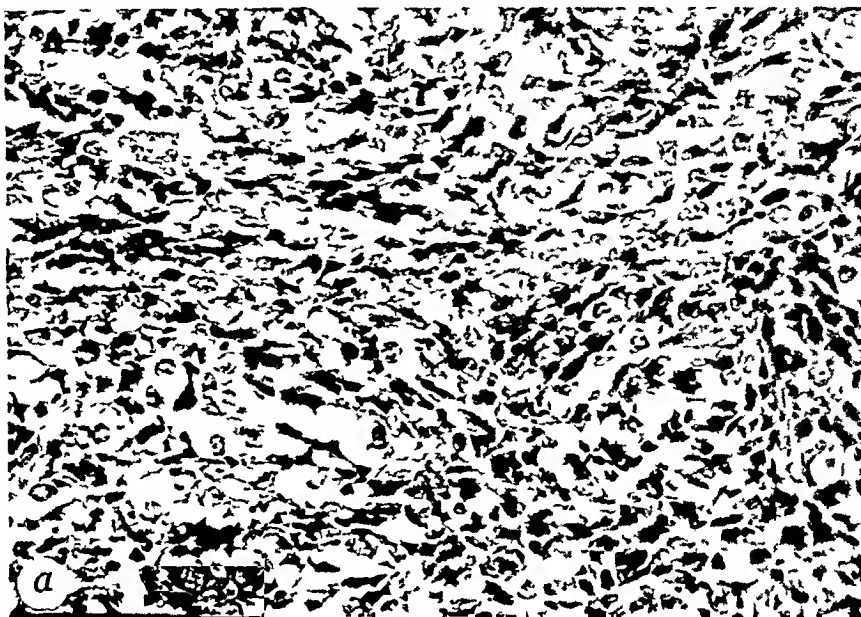


FIG 4 —Metastatic tumors in the lungs ($\times 6$)

We do not wish to discuss in detail the natural barriers which seem to exist against the process of metastasis of intracranial tumors as these are being extensively investigated by other investigators at the clinic, however, it does seem pertinent to point out the possible rôle which surgical intervention may play in the production of such metastasis. Undoubtedly, in the course of the surgical removal of a neoplasm, venous channels are opened and the intraluminal negative pressure favors the aspiration into their lumina of viable tumor cells. Thus, the tumor cells gain access to the blood stream and are carried to the lungs where they may be "filtered out" in the capillary bed, or the tumor cells, theoretically, could pass on into the arterial blood for dissemination throughout the body. This seems to have been the situation in the metastasizing tumor we have here detailed, although, to be sure, we have not excluded the lymphatics of the scalp as the portal of entry and route of metastasis nor does it seem possible to do so in this instance. Just why in most instances of operative removal of a neoplasm these sup-

posedly "viable" tumor cells do not form metastatic lesions while in rare instances they lodge and grow to reproduce the identical tissue of the primary neoplasm is not known. However, at some future day, this may be explained by certain cytochemical, cyto-electric and physical phenomena which as yet

A



B

FIG 5—Sections of hemangioblastoma removed at first operation, A, stained with hematoxylin and eosin ($\times 285$), B, stained with Perdiau's silver stain for reticulin ($\times 150$)

remain obscure to investigations. Certainly, nothing is to be gained at this time by pure speculation.

In reviewing the cases reported as cases of metastasizing intracranial neoplasms, we have collected about sixteen. A study of these reports has emphasized in our minds the difficulties one encounters in being certain that a given tumor is primary in the brain or elsewhere. Consequently we have

divided these cases into three groups (1) Those cases we do not believe have been shown to be cases of primary tumor of the brain, or we cannot be sure the metastatic tumors, if such they were, came from the brain tumor, (2) cases in which metastasis was questionable, but could possibly have arisen from tumors of the brain, and (3) cases in which metastasis was probable but not entirely certain

Group 1—Although it does not seem of much value to review those reports which occurred prior to the beginning of the era of modern methods of staining and histologic diagnosis, it has become necessary to do so, since certain cases have been reported by other authors as examples of this type of neoplastic activity. Among such cases are those of Klebs⁶ (1889) and

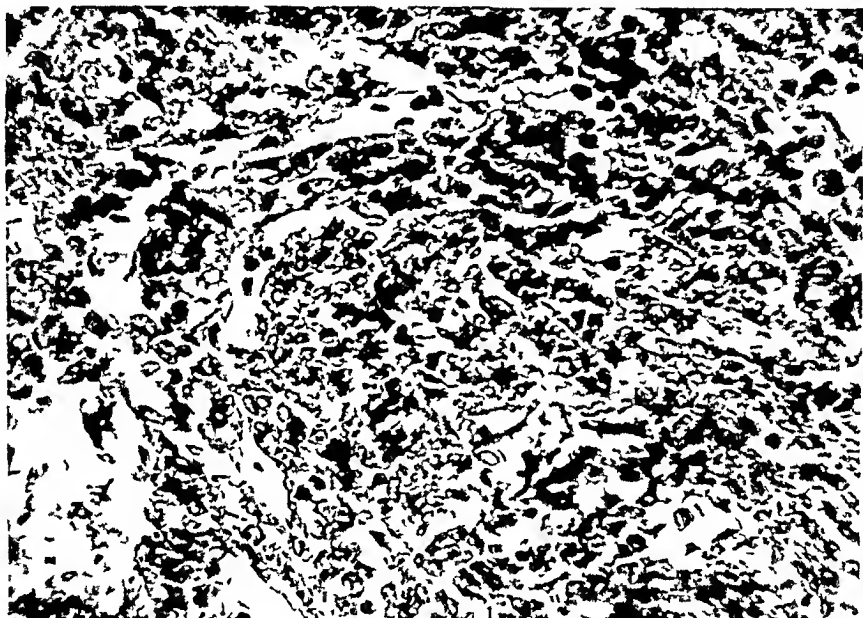


FIG. 6—Sections of hemangioblastoma removed at second operation, stained with hematoxylin and eosin ($\times 285$)

Lindner⁷ (1902). Klebs' report seems to us to have been extremely brief, to have lacked details and photomicrographs or other illustrations. Lindner's case, although reported in more detail, may well have been a case of highly anaplastic primary tumor of the urinary bladder with metastasis to the meninges (carcinomatosis?).

In more recent years certain reports based on clinical observations certainly cannot be accepted as reports of proved cases. Pendergrass and Wilbur¹⁰ (1928) failed to report any histologic examination of the metastases and in the report by Rogers, *et al*¹¹ (1935), and by Sachs, *et al*¹² (1936) there were no postmortem studies made to confirm their observations. Although Foot and Zeek¹ reported that they were unable to find any melanotic tumor nodules other than those in the lungs and meninges it is well known that such tumors metastasize early when the primary neoplasm may be ever so small. Although the patients in these cases may have had a primary

melanoma in the leptomeninges, in view of the many possible primary loci it is certainly open to considerable doubt

Group 2—In this group we include those cases in which we believe there is still a reasonable doubt that they fulfill all of the criteria for primary intracranial metastasizing tumors

It would seem to us that Davis' (1928) had fairly well proved his point were it not that his photomicrographs were not too distinct, and it is also noted that Bailey has not accepted this case as a typical case Wohlwill's¹⁵ (1930) photomicrographs are not at all convincing although his description would confirm his contention

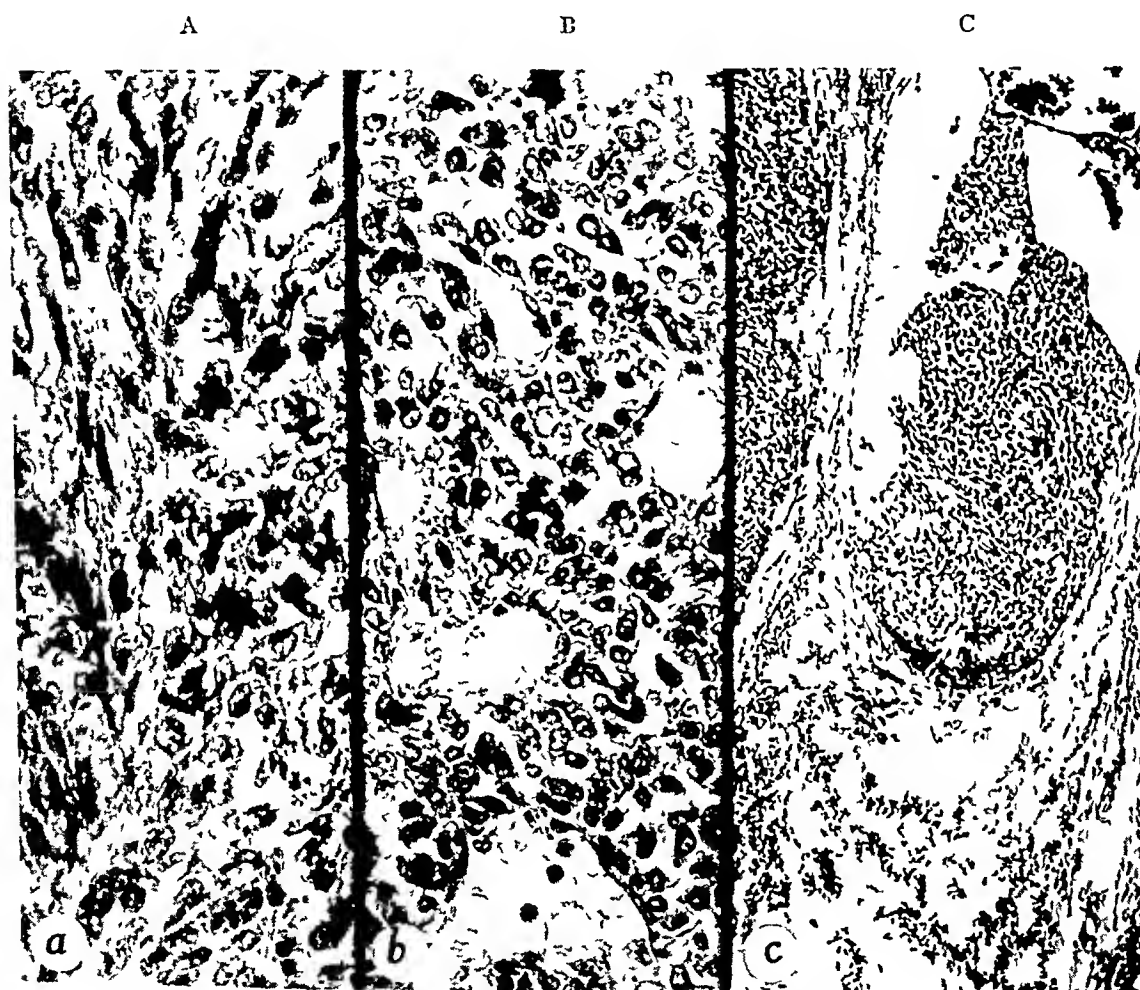


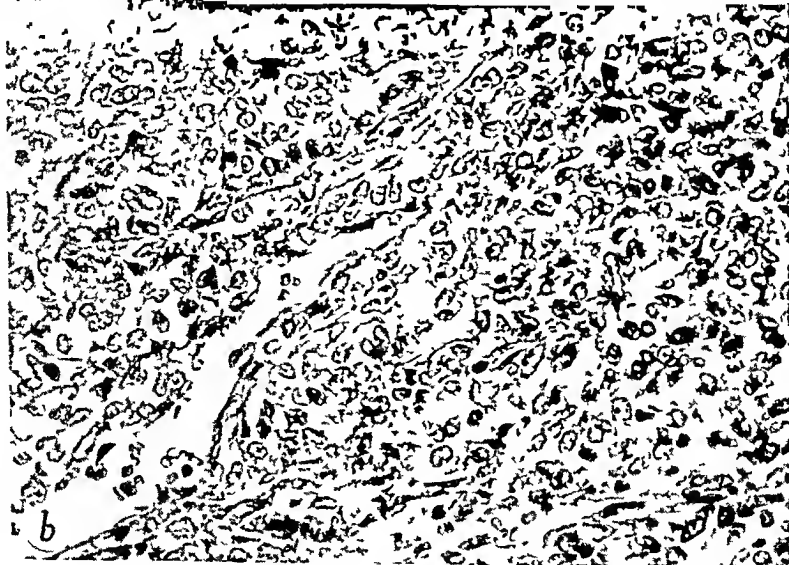
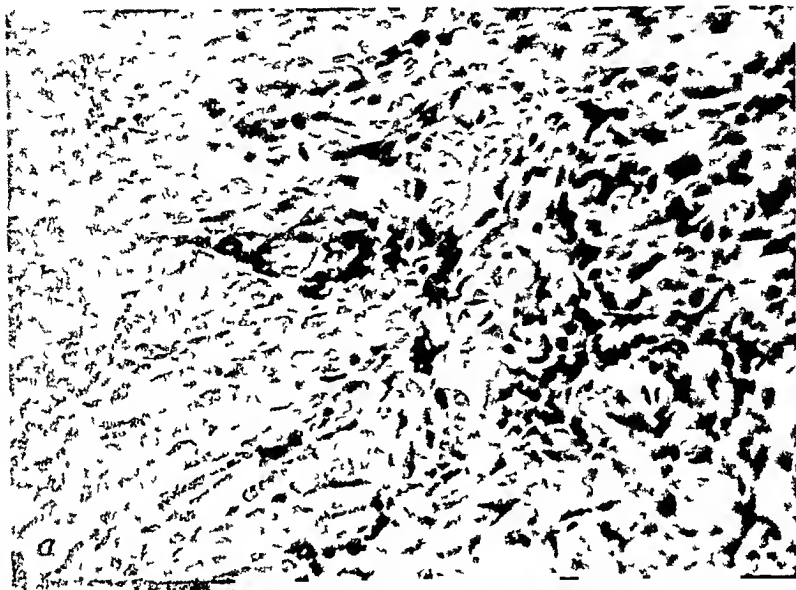
FIG 7—Sections of hemangioblastoma obtained at necropsy and stained with hematoxylin and eosin, A showing sheets and strands of cells with many mitotic figures ($\times 285$), B, showing vascular and pseudovascular channels ($\times 250$), C, showing tumor tissue partially filling a vascular channel ($\times 55$)

Brandt's¹ (1934) report was given without details and without photographic evidence to support his case In the case reported by Mittelbach⁸ (1935), the patient may well have had a highly malignant primary carcinoma of the lung, as suggested by Fischer-Wasels For this reason, we are not at all sure he has proven that this is a case of metastasizing intracranial tumor

Nelson's⁹ (1936) report is a little more convincing than some of the others, but certain inaccuracies make us hesitate in accepting his case as a case of medulloblastoma First of all the tissue obtained at the time of

the first operation performed at the clinic was examined by Dr Kernohan, and reported as inadequate for diagnosis. For that reason, he did not commit himself any further than to state that the lesion appeared to be a malignant tumor. From the photomicrographs shown in Nelson's article, we agree with Dr Bailey that it would be difficult to distinguish this tumor from a sarcoma. The question then arises as to the site of the primary neoplasm.

A



B

FIG 8—Sections of hemangioblastoma in lung, stained with hematoxylin and eosin (X285), A, arrangement of cells in sheets and strands, B, for formation of vascular channels

The case recently reported by Jurow⁵ (1941) is most interesting in that the tumor was not a malignant but apparently a benign meningioma that metastasized to the lung. It seems regrettable that the photomicrographic evidence of the pulmonary lesion was not more convincing.

Russell and Sachs¹² (Case 2) is open to some question since there was an interval of 15 years between the removal of the malignant meningioma and the appearance of the metastases in the lungs, pleura, abdominal lymph nodes and vertebra. Might the patient not have had another primary extracranial tumor which produced these metastases? In spite of the excellent description given by these authors we could not be certain of the nature of the pulmonary lesions from their photomicrographs.

Group 3—In the third group we have included the report of metastasizing tumors which we feel are, in all probability, excellent examples of primary intracranial tumors which have metastasized outside the central nervous system and its envelopes. In this group we would include the cases of

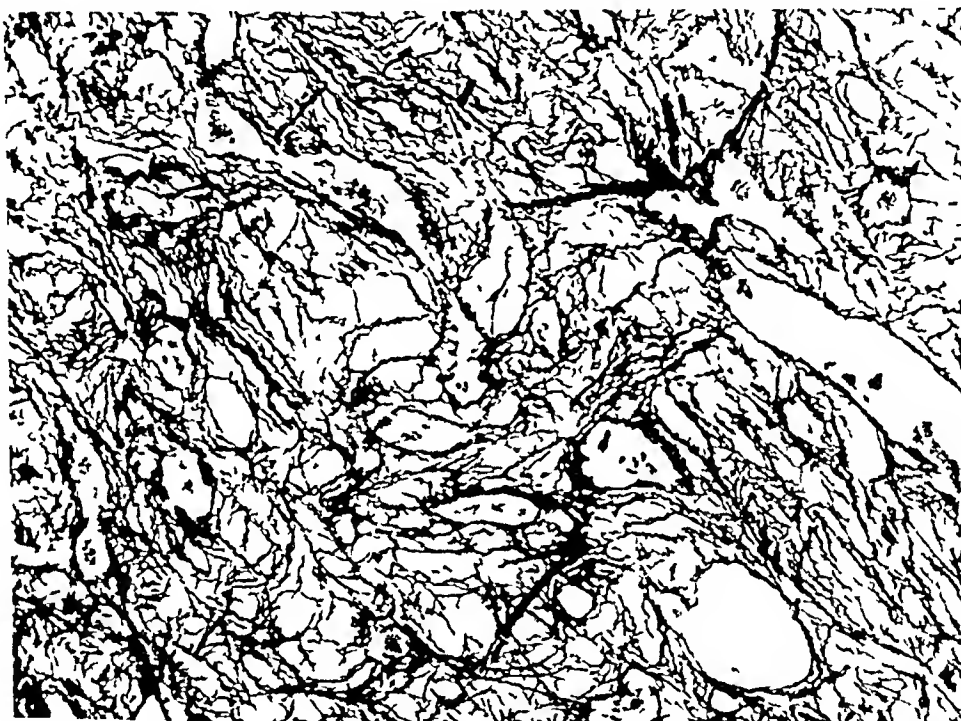


FIG 9—Metastatic tumor of lung showing reticulum pattern, stained with Perdrau's reticulum stain (x150)

(1) Cushing and Eisenhardt² (malignant meningioma), Cases 1 and 3 of Russell and Sachs ("fibrosarcoma"—malignant meningioma), and the case which we have just reported (hemangioblastoma)

Another case, that reported by Towne,¹⁴ might well belong in this group were it not for a more strict conception of metastasis. His patient had a malignant meningioma which invaded the inferior longitudinal sinus with extension into the straight, superior, right and left lateral sinuses and down into the internal jugular and innominate veins as far as the upper part of the superior vena cava. It truly was a most remarkable neoplasm. In addition, there was a report of the removal, one year previous to the patient's death, of an "endothelioma of the carotid body." This may or may not have been a metastatic nodule from the primary tumor in the brain or might have been an extension of the tumor through the wall of the left internal jugular vein!

SUMMARY

In the case of metastasizing intracranial hemangioblastoma which we have reported, the patient lived three years and nine months after the first appearance of symptoms, and one year and three months after the first surgical procedure. Sixteen cases of primary intracranial tumors which have been reported as metastasizing outside the central nervous system and its envelopes have been reviewed. Six are not accepted and seven others are accepted as possible cases of metastasizing intracranial tumors but are open to question. Another three cases are in all probability excellent examples of this type of lesion. To these three cases we have added another

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CONSERVATION OF LUNG TISSUE BY PARTIAL LOBECTOMY

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THE TRANSITION of pulmonary anatomy from an academic to an applied subject became complete when the mortality and morbidity of thoracic operations were lowered to about the same order as encountered in operative procedures elsewhere in the body. The lungs, the pulmonary lobes and the various divisions and segments of the lobes have been the objects of intensive and systematic studies by various investigators. The surgical possibilities are becoming more and more apparent as this knowledge increases.

Before anesthetic technics were perfected, assuring the safety of unhurried and precise operating in the open chest, surgeons were forced to place a premium on speed. Pulmonary resections in most cases were accomplished as rapidly as possible by mass ligation of the hilum of the lobe with the aid of a tourniquet. It was necessary, therefore, to sacrifice the entire lobe regardless of the extent of the disease. Even before researches in the surgical anatomy of the lungs eliminated the necessity of mass ligation methods in many cases, it was recognized that the five pulmonary lobes distinguished by more or less constant fissures could not be regarded as the structural units of the lungs based on the distribution of the bronchi and blood vessels. The importance of the lingula of the left upper lobe has been appreciated for many years. And the dorsal divisions of the lower lobes were considered as separate units of the lung by Ewart¹ as early as 1889. In 1934, Nelson² suggested that the lungs were made up of eight lobes. Two upper lobes, two middle lobes (the lingula of the left upper lobe was considered the left middle lobe) the dorsal divisions of the lower lobes and the basal divisions of the lower lobes (Fig 1).

An anatomic approach to pneumonectomy by separate ligation of the structures at the pulmonary hilum was first practiced by Rienhoff³ Mason,⁴ and Crafoord⁵. The technic was soon adopted widely because the incidence of successful closure of the bronchus was greatly increased. The success of the method stimulated several investigators⁶ to study the surgical anatomy of the pulmonary lobes in an effort to determine the feasibility of separate ligation of each anatomic structure when lobectomy is performed. These studies have demonstrated that in many instances and probably in the great majority of cases, individual ligation of the structures at the roots of the lobes is a feasible procedure. The technic is preferable because the incidence of severe putrid empyemas following mass ligation methods is greatly reduced.

An important contribution by Churchill and Belsey,⁷ in 1938, suggested that despite the lack of uniform and well-defined surface markings the bronchopulmonary segments might replace the lobes as the surgical units.

of the lungs They applied the principle of segmental pneumonectomy in resection of the lingula of the left upper lobe (left middle lobe) by removing the posteromedial segment of the lingula and also employed the technic in operations on the dorsal divisions of the lower lobes Subsequent experiences have demonstrated that it may be possible to conserve important amounts of lung tissue in selected cases by the extirpation of the diseased pulmonary lobules of a diseased segment rather than an entire lobe The successful application of the principle of partial lobectomy depends upon an intimate knowledge of the structural anatomy of the lung It is desirable, therefore, to review briefly the various lobes, divisions and segments of the lungs and establish the surgical and pathologic significance of each In the following discussion of the surgical units of the lung, the nomenclature proposed by Adams and Davenport⁸ will be employed

FOUR MAJOR SURGICAL UNITS OF LUNG

MEDIAL, VIEW

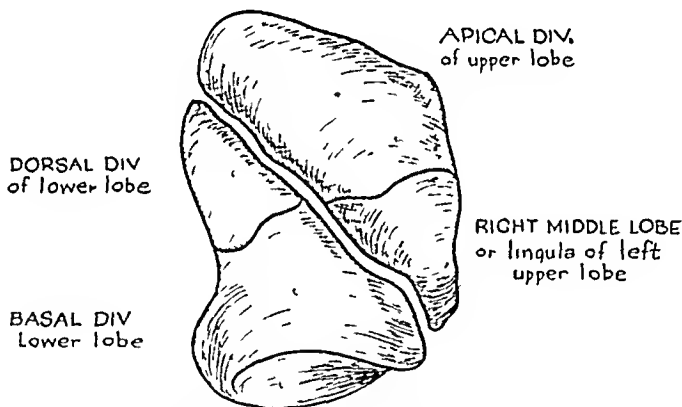
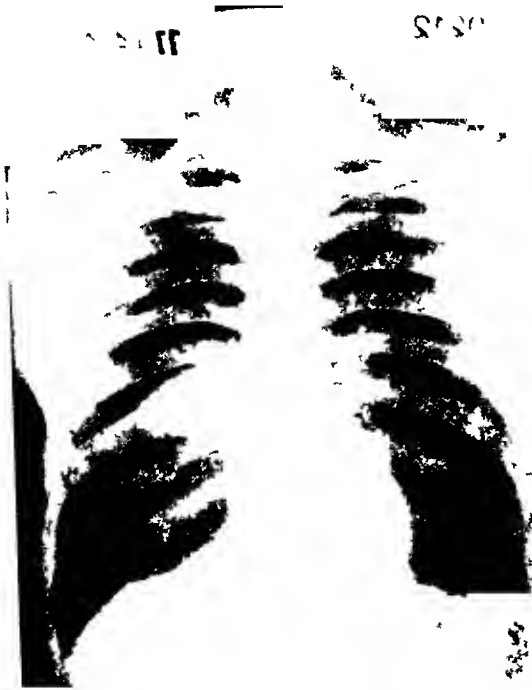


FIG 1.—Diagrammatic representations of the surgical lobes of the lung Each unit has a separate bronchus and arterial and venous channels accessible for individual ligation technic

THE STRUCTURE OF THE LOWER LOBE

Both lower lobes are composed of two divisions, namely, the dorsal and basal divisions

The dorsal division of the lower lobe is such a well-defined and constant structure that it is generally considered as a separate lobe This division of the lower lobe possesses a definite arterial and venous channel and a separate bronchus Not infrequently it is separated from the basal portion of the lower lobe by a distinct fissure, and of all the pulmonary segments it is most adaptable to separate removal Precise localization of the dorsal division segment at operation, even when the superficial markings are absent or incomplete, is not difficult because its bronchus is easily accessible and, by occluding it, a delineating atelectasis of the division can be produced The dorsal divisions of the lower lobes have special significance both surgically and pathologically since these segments are by far the most



2A



2A



2B



2B

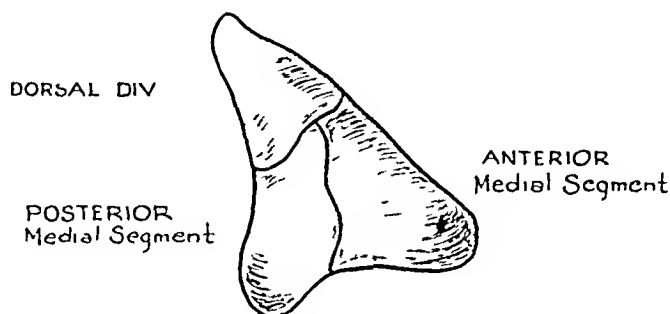
FIG 2—A Roentgenograms of the chest demonstrating a sharply localized lesion of the dorsal division of the right lower lobe

B Appearance of the chest after resection of the dorsal division of the lower lobe. The dorsal division which contained a chronic pulmonary abscess was removed alone and the entire basal division of the lower lobe saved

frequent sites of pulmonary abscess. Involvement of these divisions by bronchiectasis is rare, however, despite the predominance of bronchiectatic lesions in the basal segments of the same lobe. It becomes apparent, therefore, that if the disease is sharply localized to either division of the lower lobe the affected portion of the lobe may be removed separately (Fig 2 A and B)

SURGICAL UNITS OF LOWER LOBE

LOWER LOBE ALONE Medial View



LOWER LOBE ALONE LATERAL VIEW

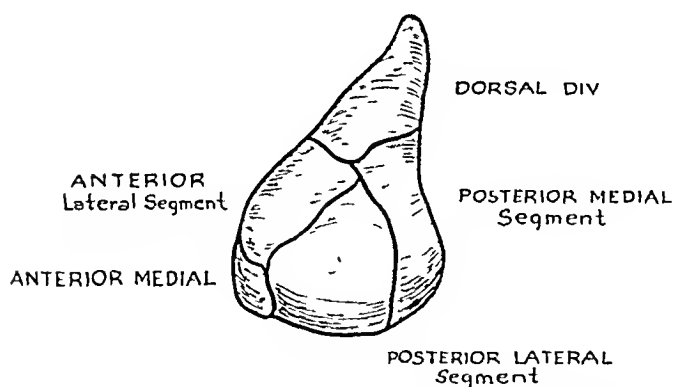


FIG 3—Schematic drawings of the lower lobe demonstrating the four segments of the basal divisions

BASAL DIVISION OF THE LOWER LOBE

The basal division of a lower lobe is divided into four fairly constant segments—anteromedial, posteromedial, anterolateral and posterolateral (Fig 3). In some cases an attempt to resect any one of the four segments in the basilar division would be impractical and dangerous. The superficial markings on the surface of the lungs are rarely sufficiently clear-cut to distinguish clearly each of the four segments, and inaccurate localization might result, in some instances, in incomplete extirpation of the diseased lung tissue. However, when both of the anterior segments or the posterior segments are

removed there is a sufficient margin of safety to insure complete eradication of a lesion confined to the periphery in an anterior or posterior position. Visualization of the lower lobe bronchus with a bronchoscope will reveal two segmental bronchi, and sometimes all four segmental bronchi can be seen. Adequate bronchography and bronchoscopic examination will establish the anterior or posterior location of the lesion. Not infrequently, one or more of the segments of the basal division will be sharply defined by rudimentary fissures. If preoperative localization places the lesion, usually bronchiectasis in the well delineated segment, excision of the single segment is safe and advantageous (Figs. 4 and 5).

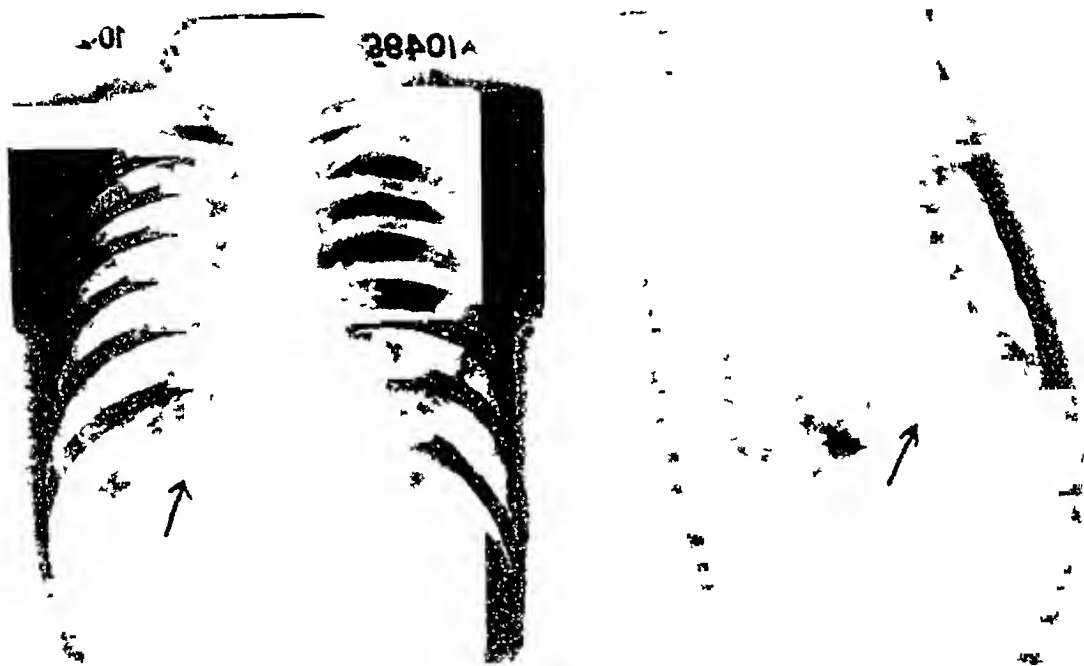


FIG. 4A.—Roentgenograms of the chest showing a sharply localized peripheral lesion of the anterior medial segment of the right lower lobe.

THE MIDDLE LOBES

For surgical purposes, the lingula of the left upper lobe may be regarded as the left middle lobe. Except for minor anatomic variations, and perhaps embryonic differences, the lingula is comparable in every respect to the right middle lobe. Both pathologically and surgically they are of the same significance. For example, the lingula is involved in more than 60 per cent of cases of bronchiectasis of the left lower lobe. The same condition is true for the right middle lobe when the right lower lobe is bronchiectatic. The boundaries of the lingula and the right middle lobe are easily identified and their bronchi are of sufficient lengths to allow individual management. They both are composed of two segments, the anterolateral and posteromedial.

Segmental pneumonectomy on the lingula division has been performed successfully by Churchill⁷ with removal of the posteromedial segment alone. It is questionable however that individual resection of either of the segments of the right middle lobe would be advisable. The segments on the right are

difficult to identify and little lung tissue would be saved. Lesions localized in the right middle lobe should, therefore, be removed by complete lobectomy. In this connection it should be stated that if there is any question concerning the amount of lung tissue to be excised the surgeon is obligated to error on the radical side. Inadequate extirpation of the diseased tissue will cast disrepute on a principle that is sound when employed properly.



FIG. 4B—Bronchogram demonstrating amputated bronchus to the anteromedial segment. The patient was suffering from intractable hemoptysis originating from localized bronchiectasis of the anteromedial segment of the lobe. The remainder of the lobe was conserved by partial lobectomy. The patient is cured, and is now on active military duty.

THE SURGICAL UNITS OF THE APICAL DIVISION OF THE UPPER LOBES

The apical divisions of the upper lobes are divided into four segments—anterosuperior, posterosuperior, anterolateral and anteroinferior.

Since tuberculosis is the predominant disease of the upper lobes, local excision of lung tissue of the anterosuperior or posterosuperior segments will not be indicated in many cases. There are, however, occasional instances when partial lobectomy of the upper lobe will obviate the necessity for total pneumonectomy. For example, bronchiectasis of the anteroinferior or lateral segments of the upper lobes may be found in association with middle lobe disease on the same side. The remainder of the upper lobe can be

saved by resection of the involved segment. Another important indication for the excision of a diseased segment in the upper lobe will sometimes be encountered in suspected bronchiogenic tumor cases. In sharply localized peripheral masses from which tissue cannot be obtained through the bronchoscope for microscopic study, excision of the local lesion should be performed before a radical operation is undertaken. Gross examination and rapid microscopic studies of the tissue may prevent the calamity of unnecessary pneumonectomy. Inspection of the surface of the lungs and palpation through intact lung tissue while usually adequate, is not wholly reliable. In



FIG. 4C—Photograph of operative incision two weeks after the partial lobectomy

our own experience, a case which presented all of the characteristic clinical features of peripheral bronchiogenic carcinoma, except a visible tumor on examination with the bronchoscope, was subjected to exploratory thoracotomy with the intention of performing a pneumonectomy. Inspection and palpation of the lung in the operating room strengthened the opinion that the lesion was a carcinoma. Local resection of the involved lung tissue and rapid histologic study, however, revealed that the lesion was inflammatory.

The hazards of exploratory thoracotomy are so insignificant that there should be no hesitation in recommending it if other diagnostic procedures have failed to establish the nature of an intrathoracic mass. The application of this principle will undoubtedly lead to earlier diagnosis and increasing numbers of successful operations for peripheral lung tumors. If, however, there is any question concerning the nature of the disease, failure to resect the local lesion before a radical operation is undertaken will constitute a grave error in judgment (Fig. 6 A and B).

REQUIREMENTS FOR PARTIAL LOBECTOMY

Certain requirements must be fulfilled if the principle of lung conservation by partial lobectomy is to be successful. First, all of the diseased pulmonary lobules must be identified and extirpated, second, the major bronchi and vessels of adjacent segments must be left intact, and third, the satisfactory repair of the raw surface of incised lung tissue must be accomplished.

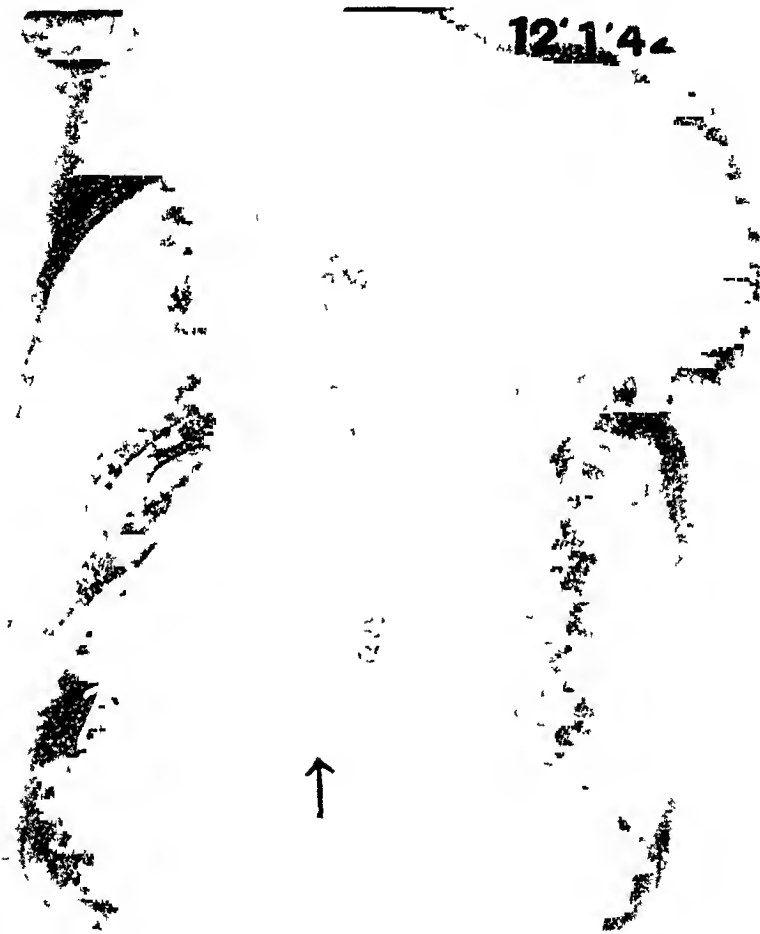


FIG 5A --Bronchogram showing sharply localized bronchiectasis of the lingula of the left upper lobe and the posteromedial segment of the left lower lobe

Precise preoperative localization of the disease with an accurate appraisal of its boundaries in terms of bronchopulmonary segments, can be accomplished by conventional roentgenograms, properly prepared bronchograms, and examinations with the bronchoscope. This information, combined with actual inspection and palpation of the lungs when the operation is undertaken, will usually localize the diseased lobules in a satisfactory manner. When the dorsal divisions of the lower lobes or the lingula of the left upper lobe are the objects of surgical attack, temporary occlusion of the bronchus to the division will positively identify its boundaries. If the bronchus to a segment is not easily accessible and it is impractical to produce atelectasis

to delineate the segment, rapid variations in the intratracheal pressure will often aid in outlining the various segments (Fig 7 A, B and C) Careful inspection of the lung surface not infrequently will reveal rudimentary fissures which become more apparent during inflation and deflation of the lung It is our impression that often the diseased segments fail to inflate as rapidly as adjoining normal segments

Transillumination of the inflated lung tissue at the operating table will, we believe, furnish another valuable aid in localizing small sharply localized lesions Further experience with this method will be necessary before its accuracy can be evaluated

When a palpable mass is encountered the simple expedient of excising it with a margin of healthy tissue is permissible This practice will not, however, eliminate the necessity of careful and complete preoperative localization of the disease

There is little danger of injuring the bronchi and blood supply of adjacent lung tissue when a diseased segment of a lobe is extirpated The rich pulmonary blood supply limits the possibilities of producing gangrene of lung tissue to ligation of major vessels or to the injudicious use of encircling ties which will occlude the blood supply to distal lobules A comparable margin of safety is also present in the bronchial tree Many of the limbs of the tree can be destroyed so long as the trunk is preserved Excision of the periphery of a contiguous segment will, therefore, cause no permanent damage

If the principle of partial lobectomy for the conservation of healthy lung tissue is generally adopted, it is safe to assume that various refinements in operative technic will develop The method I shall describe is offered as one which has proved satisfactory in a series of eight cases (removal of the lingula not included) There were no deaths and only one case was complicated by postoperative empyema Assessment of any influence on the immediate mortality of the procedure compared to total lobectomy, however, must await further experience

Morbidity and empyema become almost synonymous in a consideration of lung operations and infections of the pleura, and usually result from bronchial fistula Thoroughly satisfactory results in partial lobectomy will depend, therefore, upon the ability of lung tissue to heal after incision and suture Experimental observations by Olch and Ballou⁹ indicate that healing and scar tissue formation in the lungs is similar to that elsewhere in the body There is, in addition to laboratory observations ample clinical evidence to prove that the pulmonary parenchyma heals readily provided the

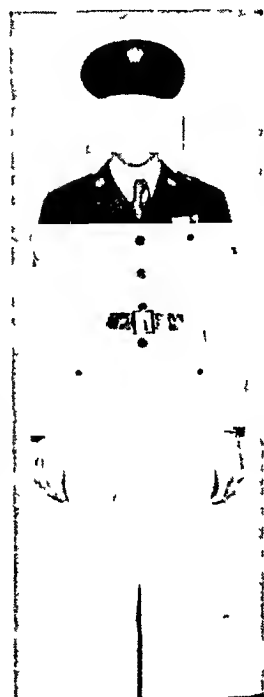


FIG 5B — Photograph of patient 18 days after lingulectomy and partial lower lobe lobectomy Despite the rather minimal amount of bronchiectatic dilations the patient was incapacitated by a chronic productive cough before the operation The soldier has returned to duty

blood supply is not destroyed and the incision is made through healthy tissue. The bronchi in the peripheral portion of the lungs are of small caliber and, unless they become fixed to the chest wall, permanent closure of the divided bronchi can be anticipated in most cases. It is in this connection that the use of a pleural graft, which will be described, is probably of great value.

OPERATIVE TECHNIC

No comment is necessary on the technic of lingulectomy. The method described by Churchill and Belsey⁷ is entirely satisfactory and generally accepted. Excision of the dorsal division of a lower lobe can usually be



6A

6B

FIG 6A—Preoperative roentgenogram of a case which was considered to be bronchiogenic carcinoma.

B—Roentgenogram of chest ten days after local resection of an inflammatory lesion. Total pneumonectomy was avoided by partial lobectomy. The haziness in the lower right chest represents a small amount of fluid and thickened pleura, the result of the thoracotomy.

effected through relatively avascular lines of cleavage after the bronchus and blood vessels are identified and secured. When the bronchus is occluded the line of demarcation between the basal and dorsal divisions will be sharply defined and the incision through the lung tissue made at this proper level. Partial excision of the basal division of a lower lobe however necessitates incisions through rather thick, vascular lung tissue. Extirpation of the diseased lobules in this location may be accomplished by placing one small hemostat at the desired position and incising the tissue below the level of the instrument. The bleeding vessels in the unclamped cut-surface of the tissue to be removed are seized separately to mark their exact positions. After the division of approximately one inch of lung tissue the line of incision is approximated and the positions of the vessels held by the proximal clamp are determined. These vessels are controlled by suture ligatures before the clamp is removed. By repeating this maneuver, the



FIG 7—A Photograph of delimiting atelectasis of antero inferior segment of the upper lobe produced by rapid inflation and deflation of the lobe
B Atelectasis of the dorsal division of the lower lobe produced by occluding the bronchus to the division
C The basal division of the lower lobe after occlusion of the basal division bronchus. Note the enormous difference in the size of the divisions when they are inflated and when they are atelectatic

segment or desired amount of lung tissue is excised. When the hemostat is removed, oozing from the cut-surface, or a vessel which has not been secured by the suture ligatures, is controlled by a few interrupted sutures of fine absorbable material. The raw cut-surface of lung parenchyma is then covered with a large graft of parietal pleura, which is obtained from the chest wall (Fig 8)



FIG 8—Drawings of pleural graft covering the line of incision through the lung tissue. Parietal pleura from the chest wall can be removed easily for this purpose.

Incision of the lung tissue by electrosurgical methods might be advantageous. This technic, however, must wait for an entirely satisfactory non-explosive anesthetic agent. The application of clamps across the lung tissue is admittedly crude, but if the instruments are removed quickly the rich blood supply of the lung apparently prevents permanent damage to adjacent lobules.

It must be emphasized that partial lobectomy should be reserved for suitable cases. The lesion must be peripheral and preoperative localization must coincide precisely with the location of the diseased lobules when the

lung is exposed at the operating table. Finally, if there is any question concerning adequate extirpation of the lesion by partial lobectomy, complete lobectomy should be undertaken. If these precautions are observed important amounts of lung tissue may be conserved successfully in selected cases.

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METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTRO-INTESTINAL TRACT¹

X—HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CANCER

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PATIENTS with gastric cancer frequently present varying degrees of emaciation which conceivably are due to a disturbed fabrication of protoplasm. Since that function is dependent upon proper protein synthesis, it is important to ascertain whether patients with gastric cancer ingest an inadequate amount of protein or have some abnormality of its metabolism.

There is considerable evidence to show that when the tissue protein stores are depleted, the serum protein levels decrease¹. Hemoglobin synthesis, nevertheless, may continue even during a period of negative nitrogen balance and at the expense of serum protein formation². Hence were protein synthesis impaired in patients with gastric cancer, they should have a high incidence of hypoproteinemia and anemia. A study, therefore, was made to determine that incidence, and to ascertain if possible the cause.

CLINICAL MATERIAL AND METHODS

The incidence of hypoproteinemia and anemia was determined among

- 1 Twenty-five healthy adults of from 20 to 65 years old
- 2 Ninety-seven patients with gastric cancer
- 3 Twenty-three patients with non-neoplastic gastric disorders. Seventeen had gastric ulcers and six had atrophic gastritis. All had anorexia and a diminished dietary intake
- 4 Twenty-one patients with nonspecific oral leukoplakia
- 5 Twelve patients who had had a gastric carcinoma removed from three months to ten years before the present study
- 6 Finally, a last group of ten patients with gastric cancer who were studied in particular to ascertain whether or not they excreted in their feces an abnormally great amount of nitrogen

No patient was studied until he had taken an adequate diet for at least two days, and was considered to be in a satisfactory state of hydration. All blood samples were obtained when the patients were in a fasting state.

The chemical methods employed in the present study have been described in previous communications of this series^{3, 4}.

Anemia was considered to exist when the red blood cell count was less

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than four million and the hemoglobin less than 80 per cent (Sahli scale, 14.5 Gm hemoglobin = 100 per cent). Concentrations of total serum protein of less than 6.6 Gm, albumin of less than 4.0 Gm, and serum globulin of less than 2.0 Gm per cent were considered abnormally low.

The criteria used to establish the existence of a dietary deficiency were (a) A history of decreased food intake as obtained from the patient or his family, or (b) observation of the dietary intake of the patient while in the hospital.

Bleeding from the gastro-intestinal tract was established by (a) A history of melena or hematemesis within six months prior to study, or (b) the demonstration of blood in the stools or gastric content after the patient had taken a meat-free diet for three days.

RESULTS

A THE EXISTENCE OF HYPOPROTEINEMIA AND ANEMIA IN NORMAL ADULTS AND IN PATIENTS WITH CARCINOMA OF THE STOMACH

1 *Normal Adults*—The total serum protein concentrations of 25 normal adults ranged from 6.6 to 7.8, and averaged 7.1 Gm per cent. Their red blood cell counts ranged from 3.8 to 5.4, and averaged 4.6 millions per mm.³, and the hemoglobin concentrations varied from 76 to 106, and averaged 91 per cent. By the criteria used, then, only one of the 25 individuals was anemic and none were hypoproteinemic (Table I).

TABLE I

THE INCIDENCE OF DIETARY DEFICIENCY, HYPOPROTEINEMIA AND ANEMIA IN THE GROUPS OF PATIENTS STUDIED

Subjects	Per Cent on In- adequate Diet	Serum Protein		Patients with Hypo- protein- emia Per Cent	Hemoglobin		Patients with Increased Hb Con- centrations Per Cent	R B C		Patients with Decreased R B C Per Cent
		Gm Per Cent			Per Cent			mil /mm ³		
		Range	Average		Range	Average		Range	Average	
25 normal adults	0	6 6-7 8	7 1	0	76-106	91	4	3 8-5 4	4 6	4
97 patients with gastric cancer	79	3 9-8 0	6 2	59	33-100	70	70	1 4-4 8	3 5	73
25 patients with nonneoplastic gastric dis- orders	100	6 05-7 15	6 6	35	67-99	85	22	3 7-5 2	4 2	22
21 patients with oral leuko- plakia	33	6 6-8 5	7 6	0	78-105	94	7	3 8-5 1	4 7	7
12 patients who had gastric cancer re- sected	25	6 7-8 1	7 3	0	63-87	75 5	25	3 0-4 8	4 4	25

2 *Patients with Gastric Carcinoma*—The results of studies on 97 patients with gastric carcinoma were in sharp contrast to those in normal individuals.

(a) *Serum Protein*—Fifty-nine per cent were hypoproteinemic. Their serum levels ranged from 3.9 to 8.0, and averaged 6.2 Gm per cent (Table I).

Of these 97 patients, the albumin and globulin concentrations were determined in the serum of 38. In these, the concentrations of albumin ranged from 2.8 to 4.9, and averaged 3.7 Gm per cent, while the concentrations of globulin varied from 1.2 to 3.0, and averaged 2.1 Gm per cent. Of those patients with hypoproteinemia, in 73 per cent that abnormality was due to a decreased concentration of the albumin fraction alone.

(b) *Anemia*—Seventy per cent of the 97 patients had abnormally low hemoglobin concentrations, and 73 per cent abnormally low red cell counts. The hemoglobin concentrations ranged from 33 to 100, and averaged 70 per cent. The red cell counts ranged from 1.4 to 4.8, and averaged 3.5 million per mm³. The anemia was macrocytic in 37 per cent, and microcytic only in nine per cent.

B. THE MOST OBVIOUS EXPLANATIONS FOR THE EXISTENCE OF HYPO-PROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CARCINOMA WERE CONSIDERED TO BE

1. *Dietary Deficiency*—Since it has been well established that the fabrication of hemoglobin and serum protein can be influenced by dietary factors,² the dietary habits of the patients with gastric carcinoma were studied.

Twenty of the 97 patients with gastric carcinoma apparently had ingested adequate diets, yet 60 per cent of these were hypoproteinemic, and 85 per cent were anemic (Table II). The remaining 77 patients had taken deficient diets, and 61 per cent were hypoproteinemic and 68 per cent were anemic. Hence, no correlation could be found between the existence of dietary deficiency and that of hypoproteinemia or anemia.

TABLE II

THE RELATIONSHIP OF DIETARY DEFICIENCY TO THE OCCURRENCE OF HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WITH GASTRIC CANCER

Number of Patients	Per Cent with Hypoproteinemia	Per Cent with Anemia
20 with adequate diets	60	85
77 with deficient diets	61	68

Although the evidence at hand indicates that the ingestion of inadequate diets could not explain the high incidence of hypoproteinemia and anemia in patients with gastric carcinoma, one could not be satisfied that the normal values used for comparison were valid controls, since the normal subjects differed considerably in age and in economic and dietary background from the patients with gastric carcinoma. It was important, therefore, to control these factors further.

Accordingly, the incidence of hypoproteinemia and anemia were determined in two other groups of patients: one with benign gastro-intestinal disorders and the other with oral leukoplakia. The patients of these groups were of an age, and dietary and economic background, similar to those with carcinoma of the stomach.

In six patients with atrophic gastritis and 17 with gastric ulcer hypo-

proteinemia existed only in 35 per cent and anemia in 22 per cent, although all of the 23 patients had taken grossly inadequate diets (Table I). Likewise, of 21 patients with oral leukoplakia, 33 per cent had been on grossly deficient diets, yet none had hypoproteinemia and only seven per cent were anemic. A comparison of these findings with those of patients with gastric carcinoma seemed to provide sufficient proof that the factors of age, dietary and economic background of the latter group were not responsible for their high incidence of hypoproteinemia and anemia.

2 *Blood Loss*—Since the fabrication of hemoglobin frequently may be at the expense of serum protein formation, the continual loss of blood from the gastro-intestinal tract conceivably might have caused both the anemia and hypoproteinemia in patients with gastric carcinoma. Of 86 patients in whom the incidence of bleeding into the gastro-intestinal tract was determined, blood loss was noted in 39. In this group, 59 per cent were hypoproteinemic, 72 per cent anemic, and 31 per cent had macrocytosis despite the fact that they had chronically lost blood. In the remaining 47 patients, who had not sustained any blood loss, 67 per cent, nevertheless, were hypoproteinemic, 74 per cent were anemic and 43 per cent had macrocytosis (Table III). Hence, there was no significant difference in the incidence of hypoproteinemia and anemia between the group of patients that had gastro-intestinal bleeding and the group that did not.

TABLE III

THE RELATIONSHIP OF CHRONIC BLOOD LOSS TO THE OCCURRENCE OF HYPOPROTEINEMIA, ANEMIA AND MACROCYTOSIS IN PATIENTS WITH GASTRIC CANCER

Number of Patients	Per Cent with Hypoproteinemia	Per Cent with Anemia	Per Cent with Macrocytosis
39 with chronic blood loss	59	72	31
47 without chronic blood loss	67	74	43

3 *The Presence of the Tumor*—The possibilities next were considered that patients with gastric carcinoma frequently had hypoproteinemia and anemia because their gastric lesions either interfered with digestion and absorption of food or induced a metabolic abnormality which impaired protein fabrication.

Measurements were made of the protein ingested and nitrogen excreted in the stools of ten patients bearing gastric carcinoma.¹⁵ All ten were found to excrete in their feces normal amounts of nitrogen (Table IV). This observation would indicate that patients with gastric cancer did not have any disorders concerned with the digestion of proteins or the amount of digested protein that could be absorbed.

Finally, none of a group of 12 patients who had undergone successful removal of their gastric tumors from three months to ten years before this study were found to have hypoproteinemia but 25 per cent still were anemic (Tables I and V). No correlation could be found between the persistence of anemia and the interval which elapsed from the time of resection. The fact that this group of patients no longer were hypoproteinemic suggests that the presence of the gastric carcinoma had initiated a disorder which prevented

the normal fabrication, utilization or distribution of serum proteins. Evidently, the impaired fabrication of hemoglobin is less often reversible.

SUMMARY

The majority of patients with gastric carcinoma studied were both hypoproteinemic and anemic. The ingestion of deficient diets and the chronic loss of blood were not sufficient explanation for the high incidence noted.

TABLE IV

THE EXCRETION OF NITROGEN IN THE FECES OF PATIENTS WITH GASTRIC CANCER

Patient	Average Dietary Protein N	Average Fecal N	
	Gm Per Day	Gm Per Day	Percentage of Protein Nitrogen Ingested
S S	9.2	0.1	3.8
R S	13.5	2.2	6.2
M M	14.6	1.1	7.3
I T	17.6	0.5	3.0
C C	30.6	1.7	5.5
R M	19.6	1.0	5.3
H P	26.1	2.1	8.5
P T	15.6	1.0	6.7
A A	16.6	0.8	4.7
I Z	18.5	1.1	5.9

TABLE V

THE OCCURRENCE OF HYPOPROTEINEMIA AND ANEMIA IN PATIENTS WHO HAD HAD A GASTRIC CARCINOMA RESECTED

Patient	Diet	Survival Period Postoper Months	Serum Protein		R B C Mil mm ³	Hemoglobin Per Cent	M C V	
			Gm	Per Cent			Cu	Micro
L B	Adequate	60	6.7		3.8	72		89
N C	Adequate	60	8.1		4.1	81		80
I C	Deficient	12	6.9		3.5	73		90
W E	Adequate	6	7.3		4.1	80		96
E P	Deficient	3	6.7		3.0	48		81
K T	Adequate	96	7.0		4.4	88		90
J Z	Adequate	120	7.1		4.2	83		90
A S	Adequate	60	7.5		4.2	85		90
M I	Adequate	16	7.9		4.8	98		90
H S	Adequate	40	7.1		4.5	90		95
P S	Deficient	31	7.6		4.5	92		90
A J	Adequate	15	7.2		4.4	85		85

Furthermore, the observation that patients bearing a gastric cancer excreted normal amounts of nitrogen in their feces argued against the possibility that the hypoproteinemia and anemia were due to a malabsorption and maldigestion of dietary protein. However, the resection of the tumor apparently improved the ability of the patients to fabricate protein, and suggested that the presence of the carcinoma had induced the existence of some metabolic abnormality which impaired protein formation. The rôle of infection around the tumor could not be ascertained in this investigation.

The cause of anemia in patients with gastric cancer certainly is not clear. It has been demonstrated in this study that the incidence and

severity of anemia is no greater among the group who had manifested gastro-intestinal bleeding, than among those who did not. Moreover, it has been the experience in this hospital that the long-continued administration of large amounts of ferrous salts and liver concentrates has not significantly affected the blood picture of patients with gastric cancer. The coexistence of hypoproteinemia and anemia in these patients, however, does suggest that the latter abnormality may be due to an impaired protein metabolism.

CONCLUSIONS

1 Fifty-nine per cent of patients with gastric carcinoma studied had hypoproteinemia and about 70 per cent anemia. No correlation could be found between the occurrence of these abnormalities and the incidence of deficient dietary intake or chronic blood loss from the gastro-intestinal tract.

2 The incidence of hypoproteinemia and anemia is considerably less in patients who have had their gastric carcinoma removed surgically.

3 The possibility is suggested that the hypoproteinemia and anemia in patients with gastric carcinoma is due to a defective fabrication of proteins.

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CONGENITAL DUODENAL OBSTRUCTION

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MAYO CLINIC

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DUODENAL OBSTRUCTION is a common lesion of adult life and is often seen as a complication of benign duodenal ulcer. Chronic duodenal obstruction which results from a congenital anomaly is rare, particularly among adults. The first case of congenital duodenal obstruction recorded is that reported by Calder,¹ in 1732. Instances of this abnormality were mentioned only infrequently in the literature until the possibility of its occurrence became rather generally recognized. Kellogg² stated that congenital occlusion of the intestines was recorded clinically 49 times in 366,000 cases, but that records of postmortem examinations placed its incidence somewhat higher. Kellogg found that in 31 per cent of cases of intestinal occlusion the duodenum is involved. The causes of congenital duodenal obstruction are usually divided into intrinsic and extrinsic causes. Among the intrinsic causative factors are atresia of the lumen, formation of a septum, and complete absence or suppression of segments. Among the extrinsic factors are included abnormal fixation of the duodenum, persistence of the hepaticoduodenocolic ligament, annular pancreas and vascular anomalies. Prenatal mesenteric cysts, tumors or cysts of the liver and pancreas are also known to cause duodenal obstruction. It is common to find associated intra-abdominal anomalies in cases in which congenital duodenal obstruction exists. Malrotation of the intestine frequently results in chronic duodenal obstruction. McIntosh and Donovan,³ and Wakefield and Mayo,⁴ have given excellent reviews of this subject, with a presentation of cases demonstrating this factor as a cause.

Duodenal obstruction secondary to a congenital anomaly is usually manifest soon after birth. If the obstruction is complete, the condition is incompatible with life and unless it is recognized and relieved, death will occur in from one to twelve days. Reports of successful surgical relief of these obstructions in early life are appearing more frequently. With partial obstruction, life may be considerably prolonged and the patient may reach adulthood. It has been stated⁵ that regardless of how long the first appearance of symptoms is delayed, these infants do not attain the development of normal children. This statement must be modified by the knowledge that in certain cases of incomplete obstruction normal development may occur. This fact is demonstrated by the case to be reported herein.

The symptoms of congenital occlusion depend largely on the degree of obstruction present. Vomiting always occurs, and is severe and persistent.

if the obstruction is complete, it may be intermittent if the obstruction is incomplete. The vomitus may or may not contain bile, it usually contains undigested particles of food and occasionally fresh blood. If, as frequently occurs, enlargement of the duodenum becomes marked, distention involving the upper part of the abdomen, most particularly the right side, and an apparent retraction of the lower part of the abdomen are present. Uncommonly peristaltic waves are visible and duodenal succussion sounds may be heard. Jaundice has been reported in cases in which the obstruction en-



FIG. 1.—Hugely distended duodenum (D). The pyloric canal (P) is widely dilated, the stomach (S) is dilated and atonic.

croaches on the ampulla of Vater. Distress may or may not be experienced. When present, it varies from a dull to a severe colicky pain simulating such abdominal lesions as appendicitis, duodenal ulcer or acute biliary disease. When pain occurs, relief is often afforded by a change in posture or by pressure on the median line below the umbilicus.

A case was recently encountered of congenital duodenal obstruction in

which an extreme degree of duodenal dilatation was attained. Despite the long-standing nature of the condition, the patient, a girl, age 16, did not have her nutrition impaired, and normal development occurred.

Case Report—A girl, age 16, gave as her chief complaint intermittent attacks of epigastric distention followed by vomiting. Her family history revealed nothing relevant. Her mother had noted that soon after birth the child suffered from frequent attacks of vomiting. She did not attach much significance to this, because long intervals of freedom often followed the episodes of vomiting, and the child developed normally. As the child grew older, it was noted that coarse foods would almost certainly cause an attack of vomiting, whereas freedom from trouble would continue for many weeks if the food ingested was soft and easily assimilated. The material vomited was always stained with bile and the quantity was always large. Often food ingested several days before could be recognized in the vomitus. Pain was not experienced at any time.

The patient's visit to the Mayo Clinic was motivated by an aggravation of symptoms, for the vomiting was becoming of daily occurrence and was preceded by increasing epigastric distention. Despite the aggravation of the symptoms, loss of weight had not occurred and the general state of nutrition was excellent.

The patient was normally developed for her age and did not appear seriously ill. She measured 63 inches (160 cm) in height and weighed 118 pounds (53.5 Kg). General physical examination gave normal results except for epigastric fullness and a succussion splash in this region. Peristaltic waves were not visible. Blood pressure 110/70. Urinalysis gave normal findings. The concentration of hemoglobin per 100 cc of whole blood was 13.5 Gm, the erythrocytes were 4,380,000 and the leukocytes 7,700. The Kline flocculation test for syphilis was negative. The concentration of blood urea and plasma chlorides measured 26 mg and 561 mg per 100 cc, respectively. The carbon dioxide combining power was 65 volumes per 100 cc of plasma. The value for serum proteins was 6.5 Gm per 100 cc and the albumin globulin ratio was normal.

A modified Ewald test meal at the end of one hour demonstrated total acidity of 18 units, absence of free hydrochloric acid, and a volume of secretion measuring 1,350 cc. A roentgenogram of the stomach and duodenum (Fig 1) revealed an obstruction in the lower portion of the duodenum, with tremendous dilatation of the duodenum. The contour of the duodenum was so huge that it exceeded in size that of the stomach. The roentgenogram of the thorax was normal.

The patient was prepared for operation by administration of a liquid diet, repeated gastric and duodenal lavage and the intravenous administration of glucose in physiologic solution of sodium chloride to which small quantities of the synthetic fractions of the vitamin-B complex and ascorbic acid were added. The total daily quantity of fluid aspirated from the stomach before operation varied from 2,300 to 5,100 cc.

Exposure through a primary upper right rectus incision revealed a hugely dilated and markedly thick-walled stomach and duodenum. When the transverse colon was retracted upward, incomplete rotation of the colon and invagination of the duodenum between the leaves of the ascending mesocolon were discovered. The first portion of the jejunum had herniated through an opening in the mesentery of the terminal portion of the ileum. There was marked obstruction of the bowel at this point. Dilatation of the duodenum extended to this point of obstruction, the bowel was normal beyond this point (Fig 2).

The lateral leaf of the ascending mesocolon was dissected free so that the bowel could be exposed, and the duodenum was dissected free down to the opening in the mesentery of the ileum. The portion of jejunum involved in the herniation was replaced and the opening in the mesentery was closed. This maneuver freed the first portion of the jejunum beyond the obstruction, and it was demonstrated that no intrinsic lesion

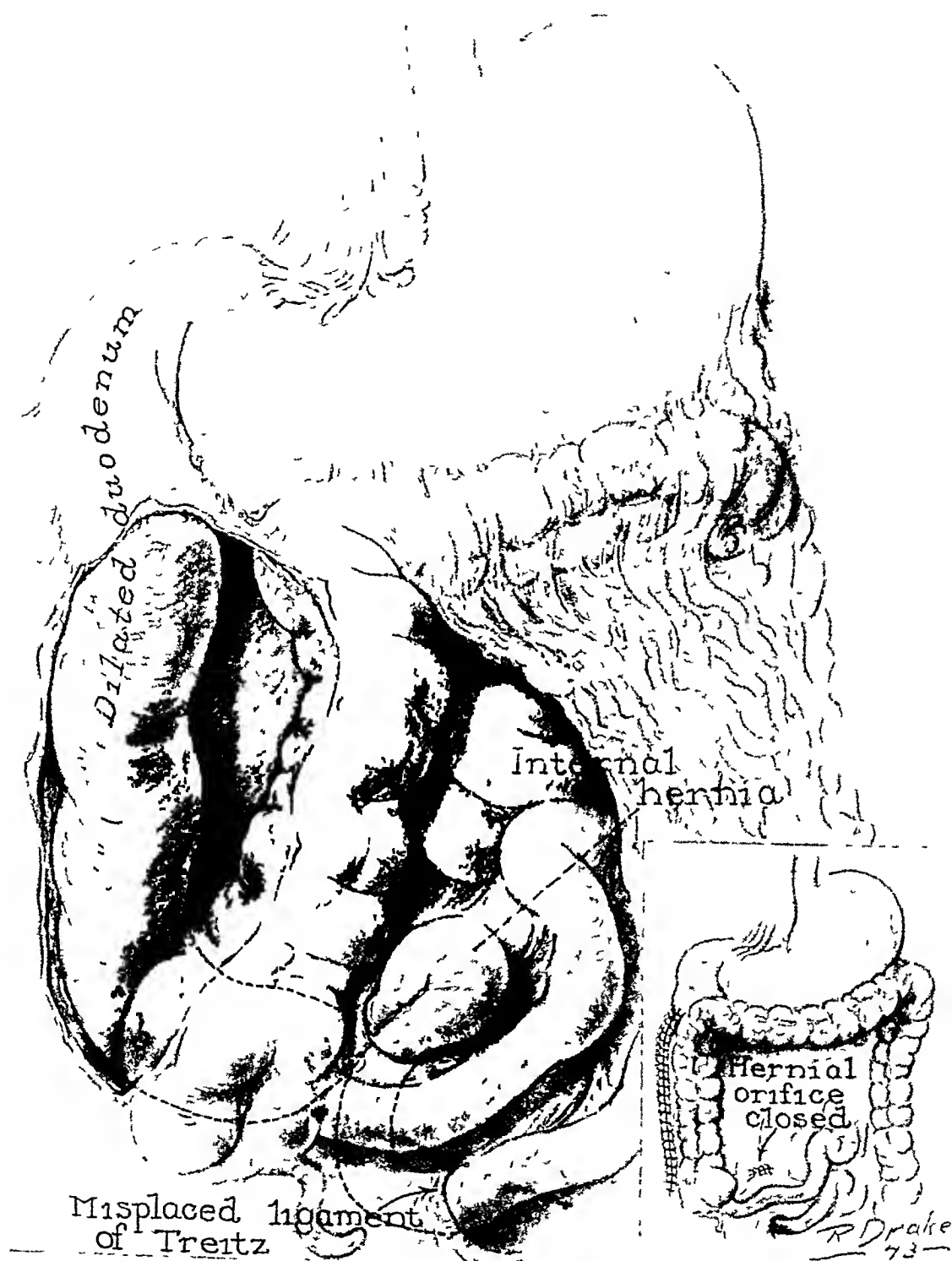


FIG 2—The appearance of the abdominal viscera at exploration. The second and third portions of the duodenum have invaginated between the leaves of the ascending mesocolon. There is incomplete rotation of the colon. Obstruction of the duodenum has resulted from herniation of first portion of the jejunum through a defect in the mesentery of the ileum. Inset: The appearance of the abdominal viscera at the completion of the operation.

existed in this portion of the bowel. A chronically inflamed appendix was removed as an incidental procedure.

Convalescence was uneventful, and when the patient was dismissed from our care, 16 days after the operation, she was free from symptoms in every way. In a communication received from her two months after the operation she stated that her

health was much improved and that she had gained approximately 20 pounds (9.1 Kg) in the interval

This case demonstrates that marked duodenal obstruction of congenital origin resulting in severe duodenal deformity need not seriously interfere with normal development. The obstruction in this instance was intermittently partially relieved, this circumstance permitted long intervals of freedom from trouble. The frequency of associated anatomic anomalies in these cases is emphasized. Incomplete rotation of the intestine was probably the fundamental developmental error which brought about the condition noted in this case.

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NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

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DIVERTICULA occur in the jejunum and ileum which are nonmeckelian in origin. Such diverticula are not exceedingly rare. At the Mayo Clinic from 1909 to 1942, inclusive, diverticula of the small intestine, exclusive of duodenal and meckelian diverticula, were observed in 122 cases. Rankin and Martin¹¹ recorded fifty-two of these cases in 1934. These 52 cases are included in the present report. Approximately 200 cases, aside from the Mayo Clinic cases, are recorded in the literature.

Although these diverticula in the jejunum and ileum are not related to the embryonic omphalomesenteric duct, the work of some investigators^{4, 25} has indicated that they may be of congenital origin. Others¹¹ have presented a variety of evidence to show that these diverticula are, in the great majority of instances, of the acquired type. It is the purpose of this paper to point out the characteristics of these intestinal outpouchings and to discuss the complications to which they may give rise.

Nonmeckelian diverticula of the small intestine occur more frequently in the jejunum than they do in the ileum. Of 122 cases in this series, in 100 the jejunum was affected. In 17 the diverticula were limited to the ileum, and in five the diverticula occurred throughout the small intestine. The proximal portion of the jejunum was most frequently affected.

These diverticula may occur in any position around the circumference of the bowel, however, the majority are situated along the mesentery. Sometimes they are actually within the mesentery, pushing the leaves of this structure apart. The diverticula vary in size from a few millimeters in diameter to large outpouchings. The larger diverticula in this series measured 8 to 9 cm. in diameter. Most of the diverticula seen had an average diameter of 1 to 4 cm. They were, in general, considerably larger than the usual tiny outpouchings seen in the colon (Fig. 1). The openings by which these diverticula communicate with the bowel vary from 1 mm. in diameter to large lumina 3 to 4 cm. in diameter.

When these diverticula are large their walls may be of "tissue paper" thinness. In such cases the wall consists merely of serosa and a very thin layer of mucosa. Small diverticula have thicker walls consisting of the usual intestinal structures.⁷ In 44 of the 122 cases only one diverticulum was observed. Thirty-seven of these solitary outpouchings occurred in the jejunum and seven in the ileum. In each of the 12 cases two diverticula were noted, and in the remaining 66 cases, three or more were present. Diverticula in other viscera were observed in 49 of 85 cases in which necropsy

was performed. Of these 49 cases associated diverticula were noted in the colon in 30 in the duodenum in 22 esophageal diverticula in two and out-pouchings of the urinary bladder in ten. In 14 of the cases in which necropsy was performed there were associated congenital anomalies such as Meckel's diverticulum malrotation of the intestines hemangioma of the liver, exstrophy of the urinary bladder and congenital pyloric obstruction.

In the 85 cases of this series in which necropsy was carried out the diverticula in the small intestine represented the probable primary cause of



FIG. 1.—Postmortem specimen obtained from a white male age 62 dead of coronary thrombosis, showing multiple large and small diverticula on the mesenteric border of the jejunum.

death in only one instance. Diverticula of the intestines were observed incidentally in all the rest. In 14 cases carcinoma of the stomach, colon, rectum, gallbladder or pancreas was present. In an additional 16, malignant disease occurred elsewhere in the body. Other associated diseases of the gastrointestinal tract and its appendages observed in the cases in which necropsy was performed, included duodenal and gastric ulcers, cholecystic disease, ulcerative and pseudomembranous colitis, cardiospasm, congenital pyloric obstruction and megacolon.

Nonmeckelian diverticula of the jejunum and ileum are noted in all age-groups (Table I). We have found the reports of only seven cases among children less than ten years of age.^{5, 6, 19, 28, 31, 35, 47} The youngest in the present series of patients was 12 years, the oldest 91 years of age. Approximately two-thirds of diverticula of the small intestine (84 of 122 cases) occurred in the male sex.

TABLE I

AGE DISTRIBUTION OF 122 CASES OF NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

Age in Years	No. of Cases
10-19	2
20-29	7
30-39	6
40-49	15
50-59	24
60-69	38
70-79	23
80-89	5
90+	2

At the Mayo Clinic most of the diverticula of the small intestine have been found at necropsy (85 cases). Some have been recognized during the course of abdominal operations (21 cases). These diverticula are not easily identified at the operating table. Even when they are distended with intestinal contents, they may offer so little resistance to the palpating hand that they will escape identification. Often they are hidden within the leaves of the mesentery.



FIG 2—Roentgenogram of small intestine following ingestion of a barium meal showing multiple large jejunal diverticula. The patient was a female, aged 47, who had had chronic ulcerative colitis for many years.

In 16 of the cases of this series the diverticula were found on roentgenographic examination of the small intestine. According to Weber,⁵⁵ if the roentgenologist is given the opportunity, he can diagnose the condition with comparative ease by roentgenoscopic and roentgenographic examination. Characteristic roentgenograms (Fig 2) are produced.

Uncomplicated diverticulosis of the small intestine does not give rise to any characteristic symptoms. In five cases of the group in which necropsy was not performed all other abdominal organs were ruled out as possible causes of the presenting symptoms by multiple roentgenographic and clinical tests. The patients in these five cases all complained of constipation, flatulence,

and abdominal discomfort. The abdominal discomfort varied from mild, indefinite abdominal aching to frequent, moderately severe attacks of pain without definite localization. These symptoms were possibly attributable to the diverticula. Edwards¹¹ has had a similar experience. He stated that abdominal discomfort and flatulence are the most common symptoms of uncomplicated diverticulosis of the jejunum. These symptoms are in no sense characteristic of any disease and are, therefore, of little aid to the clinician in the diagnosis of this condition.

Diverticula of the small intestines give symptoms when complications occur. Complicating conditions attributable to, or intimately associated with, the presence of diverticula in the jejunum or the ileum were observed in 13 of our 122 cases.

The known complications of, or associated with, diverticula of the jejunum and ileum have been compiled from our cases and those recorded in the literature (Table II). With further experience this list will undoubtedly be found to be incomplete. At present however, it represents, as far as can be ascertained, a complete summary of the observed pathologic complications of nonmeckelian diverticula of the jejunum and ileum.

TABLE II

COMPLICATIONS OF, OR ASSOCIATED WITH, NONMECKELIAN DIVERTICULA OF THE JEJUNUM AND ILEUM

- A Acute mechanical intestinal obstruction
 - 1 From enteroliths formed within diverticula
 - 2 From pressure of inflammatory mass associated with diverticulitis
 - 3 From volvulus of the intestine
 - 4 From stricture or adhesions from ancient diverticulitis
 - 5 From pressure of filled diverticula on intestine
- B Chronic intestinal obstruction
 - 1 Without apparent mechanical obstruction
 - 2 From stricture or adhesions
- C Inflammatory disturbances varying from mild catarrhal inflammation to gangrene resulting in perforation and peritonitis
- D Intestinal hemorrhage
- E Rupture of diverticulum
 - 1 Spontaneous
 - 2 Traumatic
- F Foreign bodies
 - 1 Bones etc
 - 2 Parasites
 - 3 Enteroliths
- G Neoplastic disease and formation of heterotopic tissue
 - 1 Benign
 - a Fibroma
 - b Lipoma
 - c Accessory pancreatic tissue
 - 2 Malignant
 - a Carcinoma
 - b Sarcoma

Symptoms of chronic intestinal obstruction may be associated with diverticulosis of the small intestine. A remarkable condition is thus produced, and in our cases it was the most commonly observed complication. In this condition the segments of bowel which give origin to the diverticula are markedly dilated and have thick, hypertrophied walls. The changes in the bowel are similar to those found in a loop of intestine which has been ob-

structed mechanically for a long period. In three of the six cases of diverticulosis, with symptoms of chronic obstruction of the jejunum, of this series, however, we did not observe any mechanical obstruction to which could be attributed the dilatation and hypertrophy of the segments of bowel affected by the diverticulosis. This unusual picture of "chronically obstructed-appearing" intestine and diverticulosis of the involved segments without demonstrable mechanical interference with the continuity of the bowel, may represent a "functional" type of obstruction. The following cases are illustrative.

REPORT OF CASES

Case 1—A male, age 51, entered the clinic complaining of intermittent periods of epigastric distress, flatulence and occasional abdominal distention of 20 years' duration. During the month prior to his admission his symptoms had been severe and had been accompanied by attacks of distressing pain in the left upper quadrant of the abdomen. There had not been any vomiting or obstipation. Roentgenoscopic examination of the small intestine after the patient had ingested a barium meal revealed evidence of chronic obstruction of the small bowel.

Abdominal exploration was performed, and it was found that beginning about 12 or 14 inches (30 or 36 cm) below the origin of the jejunum were multiple diverticula involving the bowel for a distance of 8 to 10 feet (2.4 to 3.0 meters). These diverticula were all on the mesenteric border of the bowel and protruded between the layers of the mesentery. They varied in size from 2 to 6 or 8 cm. They were literally studded along the mesenteric border of the intestine. Many of the diverticula had a cystic appearance and were thin-walled, almost like tissue paper, as compared with the thickened wall of the bowel itself. In all the large diverticula a distinct opening into the bowel could be felt by invaginating the wall of a diverticulum into the lumen of the bowel. In some, the opening would admit two fingers. The diverticula could be compressed easily, the air which they contained passing readily into the intestine. The jejunum was dilated to two and one-half times its normal size, and the walls were thickened and hypertrophied. A thorough search, however, did not reveal any evidence of mechanical interferences with the continuity of the bowel. The remainder of the intestinal tract, including the stomach and duodenum, was normal. A side-to-side anastomosis was made between the jejunum and the first part of the ileum. The affected portion of the bowel was thus short-circuited. The postoperative course was essentially uneventful.

In the following case the condition was similar to that of Case 1, but more extensive and advanced, the duodenum also being involved in the pathologic process. The extreme difficulties of the radical surgical cure of the condition are well emphasized.

Case 2—A male, age 45, entered the clinic complaining of having had intermittent, progressively more severe and frequent attacks of nausea, vomiting, cramping upper abdominal pain, borborygmus and looseness of the bowels. He had lost 30 pounds (13.6 Kg) and was quite weak. On one occasion he had vomited a large quantity of dark blood. Roentgenoscopic examination of the small intestine after the patient had ingested a barium meal showed evidences of obstruction of the duodenum and duodenal diverticulosis.

Abdominal exploration was performed and many diverticula were found along the mesenteric aspect of the upper five feet (1.5 meters) of jejunum and in the duodenum. Many of these were as large as an "adult's fist" and extremely thin-

walled. The duodenum and upper part of the jejunum were markedly dilated, up to four inches (10 cm) in diameter, and their walls were thick and hypertrophied. Thorough search, however, did not reveal any mechanical obstruction. The common bile duct emptied into one of the large duodenal diverticula. A short-cutting procedure was impractical. Resection of the involved portion of the bowel was performed. The common duct was explored, its opening into one of the diverticula ascertained, and its connection with this diverticulum severed close to the ampulla of Vater. The second and third portion of the duodenum and the upper five feet (1.5 meters) of

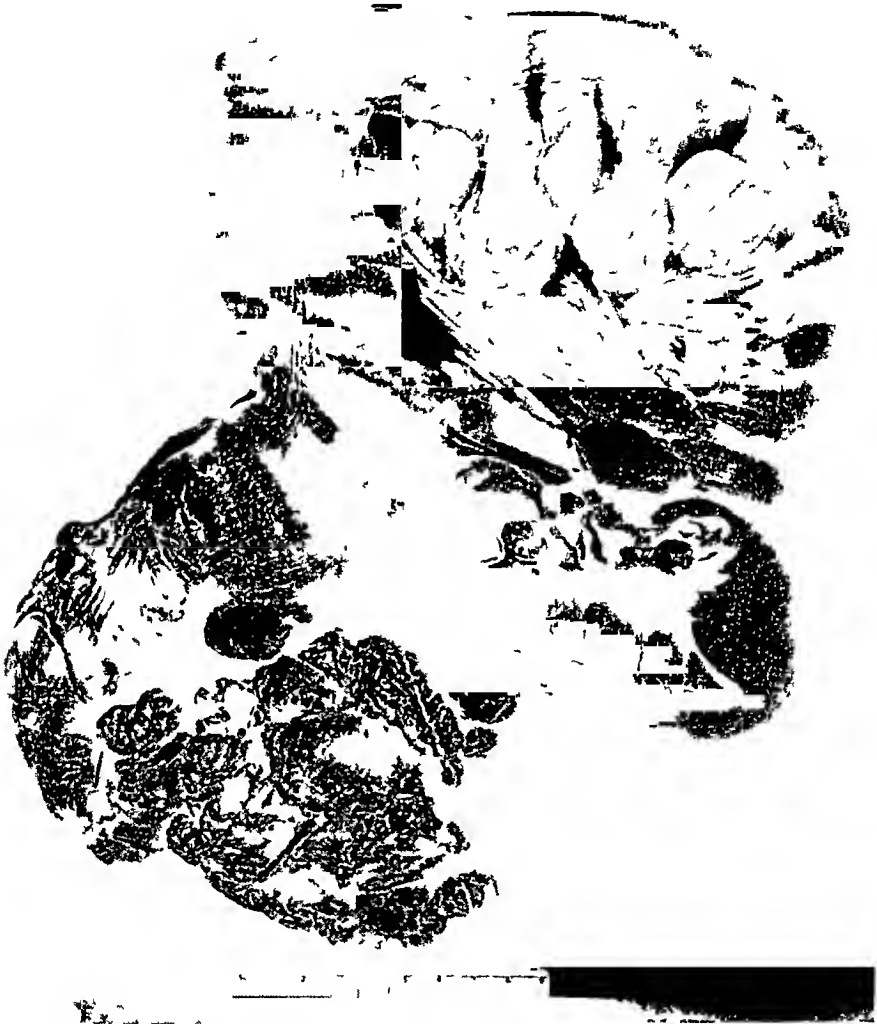


FIG. 3.—Case 2. Diverticulosis and chronic obstruction of the jejunum. Surgical specimen, 1.45 m. in length, consisting of a portion of duodenum and proximal jejunum. The bowel is markedly dilated and hypertrophied. Many thin-walled diverticula are present on the mesenteric border. No mechanically obstructing lesion was observed.

the jejunum were included in the resection. The ends of the duodenum and the jejunum were inverted and antiperistaltic anterior gastrojejunostomy (side-to-side) was performed. The end of the common bile duct was then implanted into the blind end of the jejunum which projected beyond the gastrojejunal stoma. The common bile duct was drained with a T-tube. The operation was difficult because of the friability of the bowel and the tendency of the tissue paper-like walls of the divertic-

ula to rupture after the slightest trauma and contaminate the peritoneum. The patient expired 24 hours after operation. Postmortem examination was not obtained.

A photograph of the pathologic specimen is reproduced in Figure 3. The segment of bowel removed measured 145 cm in length. The diverticula varied in size from 1 to 8 cm in diameter.

In the preceding cases extensive mesenteric diverticulosis was considered the cause of the changes in the bowel by interfering in some way with the nerve supply or mechanically with the function of the intestine. The following case, however, demonstrated that the same type of "chronically obstructed-appearing" bowel may be observed when only one diverticulum is present. This would seem to indicate that the disturbance of intestinal function leading to dilatation, hypertrophy and thickening of the intestine is not always explained adequately by the presence of the diverticula. The diverticulosis is probably a phenomenon of secondary importance.

Case 3—A female, age 63, came to the clinic complaining of progressively more severe constipation of many years' duration. For one year prior to admission constipation had been relieved only by large doses of cathartics, and there were frequent attacks of gaseous abdominal distention and cramping abdominal pain. In the three months immediately preceding admission several episodes of severe abdominal distention and cramps, obstipation and repeated emesis had occurred. Roentgenographic examination of the stomach, small intestine and colon did not reveal any definite evidence of obstruction. The rate of passage of ingested barium through the small intestine was delayed, however, the opaque meal reaching the cecum in 72 hours.

Abdominal exploration was performed. There were many adhesions between the abdominal wall and the hepatic flexure of the colon at the site of a former cholecystectomy. There was no demonstrable mechanical obstruction of any portion of the intestinal tract. A portion of the jejunum was dilated to about three times normal size, and its walls were thick and hypertrophied. This obstructed appearance of the bowel began at the duodenojejunal angle and continued for about two and one-half feet (76 cm). Distally, the bowel was perfectly normal in appearance. There was one diverticulum, the size of an English walnut approximately in the middle of the dilated segment of jejunum. No evidence of inflammation about this diverticulum or of mechanical interference with the intestinal lumen by the diverticulum could be found. The adhesions about the gallbladder were separated and the abdomen was closed. The postoperative course was uneventful.

Though the relation of the diverticulum to the intestinal changes is not understood in the foregoing case the diverticulum must in some way have played an important part in the pathologic changes seen in the bowel. A similar segmental change in the small intestine, consisting of hypertrophy and dilatation without diverticulosis is practically an unknown condition.²¹

In the following cases mechanical obstruction of the bowel was demonstrable.

Case 4—A male, age 64 entered the clinic complaining of loss of appetite and of weight. He had had an operation for intestinal obstruction five years prior to admission. He had had anorexia for one year and had lost 20 pounds (9.1 Kg). During the two weeks immediately preceding his coming to the clinic he had vomited repeatedly. Roentgenoscopic examination of the small intestine showed evidence of an obstruction lesion in the upper part of the jejunum.

Celiotomy revealed the duodenum and a portion of the adjacent jejunum to be

markedly dilated and to have thickened walls. There were multiple diverticula present in the mesenteric aspect of the dilated portion of jejunum. These varied considerably in size (Fig 4), the largest being 7 to 8 cm in diameter. Further exploration revealed multiple adhesions between the loops of jejunum, which were dilated and the site of diverticulosis. Some of these adhesions definitely constricted the intestinal lumen but at no point was there complete intestinal obstruction. The adhesions were freed, the appendix was removed, and the abdomen closed. During the immediate postoperative course there was intestinal obstruction which soon subsided after conservative treatment. After the first postoperative week, convalescence was normal.

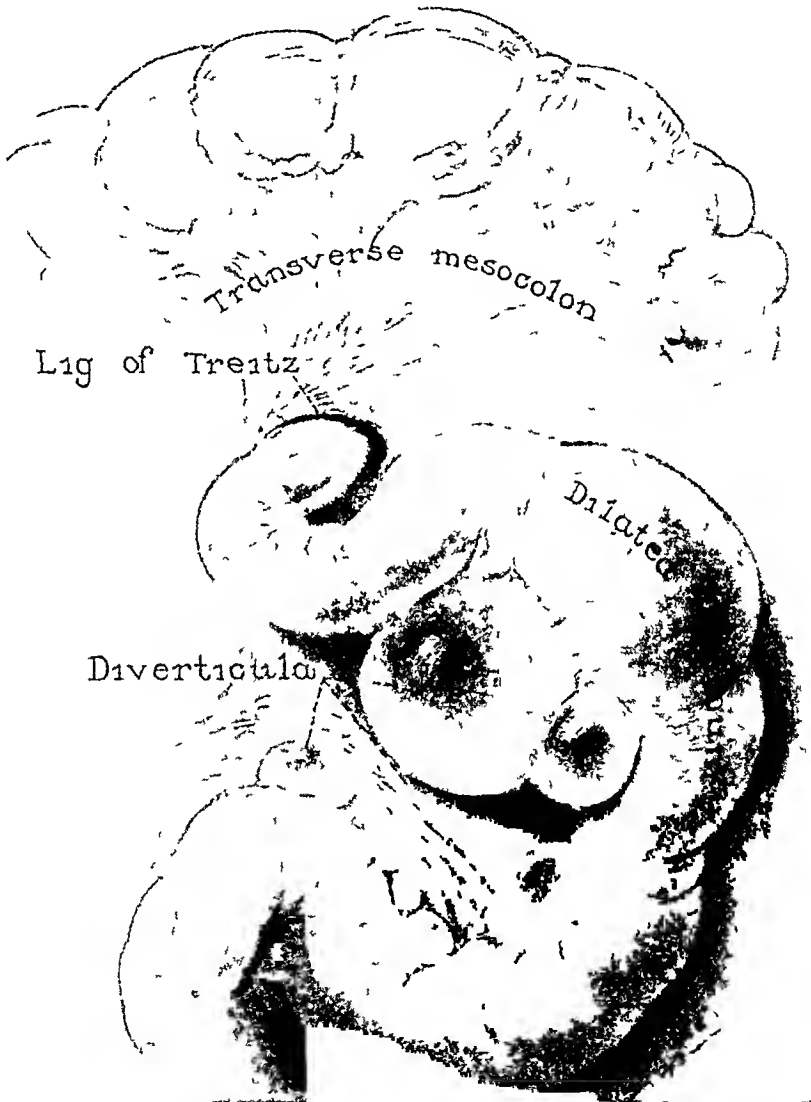


FIG 4—Case 4. Diverticulosis and chronic obstruction of the small intestine, showing dilatation and thickening of the intestinal wall. Multiple diverticula are present on the mesenteric aspect. Obstruction resulted from adhesive bands.

Case 5—A male, age four, entered the clinic with the history and findings of recurrent intestinal obstruction. Celiotomy for intestinal obstruction and adhesions had been performed twice prior to admission. After a period of observation, further surgical treatment for recurring obstruction of the small bowel was advised. The parents decided to try medical management.

Nine years later the patient returned to the clinic, with a history that he had been constantly an invalid because of repeated attacks of intestinal obstruction. His general state of health was very poor. He now accepted surgical treatment.

Celiotomy was performed. The entire intestinal tract was observed to be "firmly bound down by many dense adhesions." The jejunum was dilated and had thickened walls. On the mesenteric aspect of this dilated portion of bowel were many diverticula, some of which were 6 to 7 cm in diameter. These large diverticula were extremely thin-walled and friable. The adhesions that were kinking and obstructing the small bowel were sectioned as completely as possible, and the abdomen was closed. The patient expired on the nineteenth postoperative day of peritonitis and exhaustion.

Case 6—A male, age 72, came to the clinic complaining of dyspnea, cough, flatulence, intermittent abdominal distention and constipation. Roentgenologic studies of the stomach and colon gave negative results. Roentgenoscopic examinations of the small intestines revealed extensive diverticulosis. Multiple small and large diverticula were observed in the duodenum and jejunum, the largest being about 6 cm in diameter. In addition, the jejunum was moderately dilated as though chronically obstructed. No definite obstructing lesion could be visualized. Because of the patient's age, the associated pulmonary disease and the nonemergent character of the abdominal symptoms, operation was not advised.

Spontaneous perforation of a diverticulum of the jejunum or ileum may occur. Several such cases have been recorded in the medical literature^{7, 10, 11, 16, 17, 31, 48, 52}. In these there is sudden severe abdominal pain followed by the signs and symptoms of rapidly spreading peritonitis. Death ensues quickly unless the surgeon intervenes and closes the perforation. The following case is illustrative.

Case 7—A female, age 57, underwent cholecystectomy and exploratory choledochostomy for subacute cholecystitis supervening on chronic cholecystitis, as well as for cholelithiasis and subacute pancreatitis. The postoperative course was marred by a low-grade febrile reaction for the first seven days but aside from this, progress was essentially satisfactory until the ninth day. On the ninth postoperative day the patient was seized suddenly with severe abdominal pain. The signs of rapidly spreading peritonitis became evident and death ensued within 48 hours.

At necropsy, diffuse purulent peritonitis was observed. There were five diverticula in the jejunum, each of which measured 2 to 3 cm in diameter. In four of these outpouchings there was no evidence of pathologic change. The wall of the fifth, however, was necrotic and contained a perforation 5 mm in diameter. There was, in addition, an abscess of the capsule of the liver. This abscess had ruptured. On microscopic examination of this diverticulum it was observed that the walls were necrotic and infiltrated with inflammatory cells.

Benign tumors of nonmeckelian diverticula of the jejunum and ileum have been recorded very rarely in the literature. Biandes⁵ has reported the occurrence of a lipoma in association with a jejunal diverticulum. Other instances in the literature have not been found. Our series contains one fibroma of an ileal diverticulum and, in another case, the formation of heterotopic tissue in a jejunal diverticulum (accessory pancreas).

Case 8—A male, age 34, died of pulmonary complications after ileostomy had been performed as a first step in the surgical treatment of megacolon. At necropsy several diverticula were observed on the mesenteric border of the terminal portion

of the ileum. The largest diverticulum was 3 cm long and 1 cm in diameter. One of these diverticula was completely filled with a globular mass which measured 4 cm in diameter. Histologic examination of this tumor revealed it to be a benign fibroma. It had its origin in an ileal diverticulum (Fig 5).

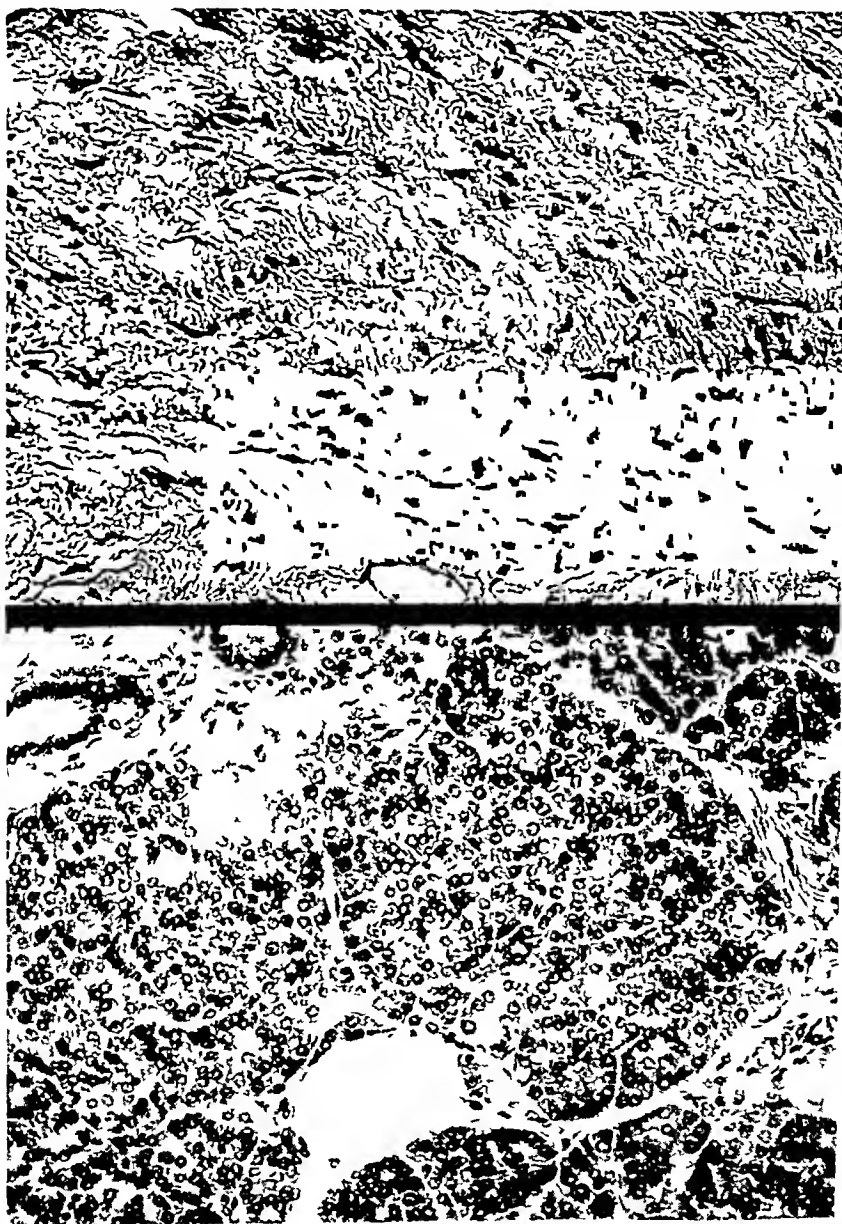


FIG 5—Case 8. Fibroma originating in a nonmeckelian ileal diverticulum ($\times 175$).

FIG 6—Case 9. Pancreatic heterotopia. Typical pancreatic tissue found in the tip of a large jejunal diverticulum ($\times 175$).

Case 9—A female, age 54, died after total abdominal hysterectomy for carcinoma of the fundus uteri. At necropsy, a solitary diverticulum, measuring 5 by 4 cm, was found on the mesenteric aspect of the upper part of the jejunum. In the tip of this outpouching there was a small firm tumor. Microscopic examination of this nodule showed it to be composed of typical pancreatic tissue (Fig 6). The condition was aberrant pancreas in a jejunal diverticulum.

Diverticula of the gastro-intestinal tract, in general, do not show any particular or unusual tendencies to undergo malignant degeneration. In the small intestine both primary carcinoma and diverticula are rare. Morrison and Feldman¹⁶ have recorded an instance of a primary carcinoma in a duodenal diverticulum. Nygaard and Walters,³⁸ in a thorough review of the literature in 1937, were able to collect six instances of carcinoma and four of carcinoid tumors which had as their primary site a meckelian diverticulum. To the present, however, no undoubted instance of primary carcinoma of a nonmeckelian diverticulum of the jejunum has been recorded. The following protocol, therefore, significantly records such a case.

Case 10—A male, age 27, came to the clinic complaining of progressively more severe attacks of cramping pain in the lower part of the abdomen associated with anorexia, vomiting and occasional diarrhea. He had lost 20 pounds (9.1 Kg). A tumor was palpable in the left lower abdominal quadrant. The concentration of hemoglobin was 9.8 Gm per 100 cc of blood.

Abdominal exploration revealed an irregularly rounded, tumorous mass, the size of an orange, in the left lower portion of the abdomen. This tumor was intimately attached to the mesenteric wall of the midportion of the jejunum but did not extend into the lumen of the bowel. It was contained in a large, solitary diverticulum of the jejunum. There were a number of enlarged lymph nodes in the omentum and in the mesentery of the involved portion of bowel. There was, however, no palpable evidence of extension of the growth into the liver pelvis or other regions, nor was there any evidence of a primary malignant lesion elsewhere within the abdomen. Resection of the involved segment of jejunum along with the tumor, a generous portion of the mesentery and practically all of the omentum was performed. Both ends of the jejunum were closed, and the continuity of the lumen was obtained by a side-to-side anastomosis. The postoperative course was uneventful and 22 months later the patient reported that he was in excellent health.

Photographs of the pathologic specimen are presented in Figure 7. The tumor measured 8 by 8 by 4.5 cm. It had had its origin in a large diverticulum on the mesenteric wall of the jejunum. It completely filled the diverticulum but had not extended into the wall or lumen of the bowel. Histologic examination proved it to be a small cell adenocarcinoma, Grade 4 (Broders).

In Meckel's diverticula sarcomata are of more frequent occurrence than carcinomata according to Nygaard and Walters.³⁸ These authors in 1937 were able to collect fifteen instances of sarcomata arising in Meckel's diverticula. No case of primary sarcoma of a nonmeckelian diverticulum of the jejunum or ileum has been established as yet, the nearest approach to it being the following case in which a leiomyosarcoma was observed in association with a diverticulum.

Case 11—A male, age 47, came to the clinic complaining of indefinite abdominal symptoms. After inconclusive examination abdominal exploration was performed. About four inches (10 cm) distal to the ligament of Treitz a tumor 2.5 cm in diameter was observed on the mesenteric aspect of the jejunum. About six inches (15 cm) below this on the mesenteric border was a jejunal diverticulum about 2.5 cm in depth. A segmental resection of that portion of the intestine which contained both the diverticulum and the tumor was performed. Histologic examination of the tumor

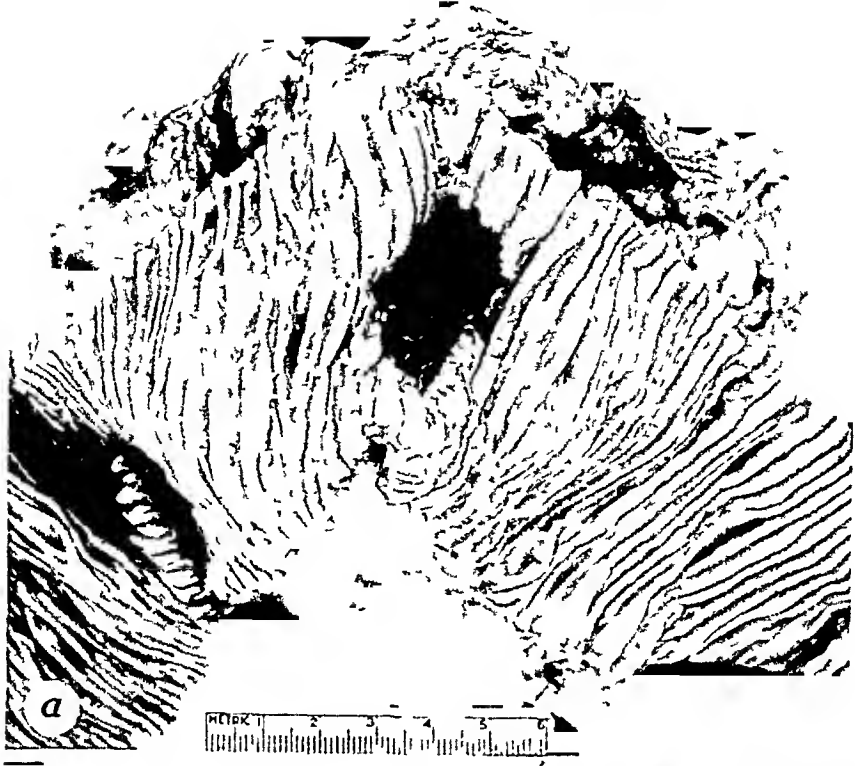


FIG 7—Case 10 Primary carcinoma of a jejunal diverticulum *a* Inside view with jejunum opened along line of attachment of its mesentery, showing opening into diverticulum, *b*, lateral view showing mass of malignant tissue filling the diverticulum, *c*, small cell adenocarcinoma, Grade 4 (Broders) ($\times 80$)

showed it to be a leiomyosarcoma, Grade 1 (Broders) This sarcoma had not arisen in a diverticulum

This case is presented because of the association of the two conditions, jejunal diverticulum and leiomyosarcoma

COMMENT

Acute mechanical intestinal obstruction is the most commonly reported complication of nonmeckelian diverticula of the jejunum ^{3, 4, 6, 9, 12, 14, 16, 18, 20, 23, 27 30, 32, 33, 37, 40, 42, 46, 49, 51, 53, 54, 56} Obstruction of the intestine may result from the formation of enteroliths within diverticula, from pressure of an inflammatory mass associated with diverticulitis, from volvulus of the bowel initiated by diverticula, from stricture or adhesions produced by recent or ancient diverticulitis, or from the pressure of large filled diverticula on the adjacent bowel

In the case reported by Christ⁹ the obstruction was caused by a large mushroom-shaped coprolith, 6 x 4 x 3 cm, which had been displaced from a diverticulum and was unable to pass through the ileum Enterotomy was performed, and the patient recovered

Stiven⁴⁹ has recorded an instance of volvulus which was caused by the interlocking of a large diverticulum in the terminal ileum, with a diverticulum of similar size which originated from the proximal jejunum The necks of the two diverticula were twisted, causing a band, over which a loop of small intestine was kinked and obstructed The volvulus was freed and the patient recovered

Gordimer and Sampson's²³ case illustrates the intestinal obstruction that may result from diverticulitis At celiotomy upon a female, age 45, a severely inflamed diverticulum was found, which was producing adhesions and obstruction of the intestine This diverticulum was excised and a drainage tube inserted The patient recovered

Diverticulitis does not always produce intestinal obstruction, however, Inflammatory disturbances of jejunal and ileal diverticula may vary from mild catarrhal inflammation to gangrene, producing perforation and peritonitis In the cases of our series in which necropsy was performed, there were two instances in which mild catarrhal inflammation of jejunal diverticula was observed on routine examination If the diverticulitis gave any symptoms in these two cases they were overshadowed completely by the more serious disturbances which led to fatal terminations It seems likely, however, that such mild inflammations of diverticula might give rise in otherwise healthy persons to signs and symptoms of an inflammatory intra-abdominal disease Only severe diverticulitis will produce symptoms and signs urgent enough to warrant abdominal exploration The literature contains several such reports ^{2, 7, 11, 15, 22, 23, 44, 56}

It is surprising, in view of the thinness of the walls of many of these diverticula of the jejunum and ileum, that rupture does not occur more

often than is observed. Only a few cases have been recorded in the literature.^{1, 5, 15} The report of Butler and Weedon⁵ is illustrative. A male, who had always been previously well, was kicked in the abdomen by a horse. Urgent signs of a serious intra-abdominal disturbance made their appearance immediately, and celiotomy was performed. At operation a ruptured intra-mesenteric diverticulum was found and closed. The patient died ten hours after the operation. At autopsy, an additional ruptured diverticulum which had escaped observation at operation was found.

Hemorrhage may occur from nonmeckelian diverticulum of the jejunum and ileum.^{24, 26, 37, 50} The loss of blood thus sustained may be so severe as to demand appropriate intervention.²⁴

Foreign bodies may become lodged in the diverticula. Examples of retained ingested bones,⁹ food particles,^{5, 2} enteroliths,^{9, 12, 51, 54, 57} and parasites^{22, 1} have all been reported.

Uncomplicated and asymptomatic diverticulosis of the jejunum or ileum does not require surgical treatment. In evaluation of symptoms of diverticulosis, all other possible causes of the complaints must be ruled out, for as we have pointed out, the outpouchings are usually silent, and the patient's distress may be due to an unsuspected disease of the gallbladder, stomach or colon. To date no patient upon whom the diagnosis of uncomplicated diverticula of the jejunum or ileum has been made has been operated upon at the clinic for the relief of the condition.

When acute complications such as intestinal obstruction, diverticulitis or rupture of a diverticulum present themselves surgical treatment is often imperative. In operations upon such cases it is probably best to limit surgical treatment to relief of the urgent condition.

An attempt at surgical elimination of the diverticula is justified when persistent distressing symptoms, the syndrome of diverticulosis and chronic obstruction, or other chronic complications are present. As a rule, entero-enterostomy, side-tracking the involved segment is preferable to resection and anastomosis in one stage unless the diverticula are localized to a small segment. These patients are often poor surgical risks. There is also a distinct danger of rupturing one of the fragile thin-walled diverticula during an extensive operative procedure. A short-circuiting procedure alone may relieve the patient of his symptoms. If not the involved segment may be resected with less risk at a later date.

SUMMARY

One hundred twenty-two cases of nonmeckelian diverticula of the jejunum and ileum are reviewed. The anatomic and clinical characteristics of these diverticula have been presented. A complete list of the observed pathologic conditions to which such diverticula may give rise is presented. The syndrome of diverticulosis and chronic obstruction of the small intestine is described but is not considered to be characteristic. The first reported case of primary

carcinoma of a jejunal diverticulum is contained herein, along with several other unique and interesting complications of nonmeckelian diverticula of the jejunum and ileum

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DERMOID CYST OF PANCREAS

CASE REPORT

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DERMOID CYSTS are congenital abnormalities the origin of which is linked with disturbances of embryonal development. Within the cyst wall are generally found copious quantities of thick, oily, sebaceous material matted together with hair and teeth.

Although the dermoid cyst is a fairly common anomaly of the ovary, it has been reported in other parts of the body with varying degrees of frequency. Some of these locations have been very strange. Dermoid cysts have been found in the scalp, skull, face, neck, pharynx, thymus gland, hypophysis, brain, meninges, mediastinum, mesentery, omentum, peritoneum, spinal cord, testes, bladder and spleen. They have also appeared in the orbital, meso-branchial, pre-sternal, retroperitoneal and sacrococcygeal regions.

The paucity of occurrence of dermoid cyst in the pancreas is evidenced by the fact that not a single case has been reported within the past 20 years. Survey of the literature revealed but two such cases reported. It is felt, therefore, that it may be of interest to review these cases and present the pertinent findings in the case herewith reported from the DeCourcy Clinic.

Judd,¹ in 1921, in a report of 41 cases of pancreatic cyst, included a single case of dermoid cyst. Clinical data abstracted from Masson and Caylor's² detailed report of this case revealed that the patient was a 33-year-old female who had complained of weakness, backache and growth in the left upper portion of the abdomen. This growth had been enlarging gradually for nine years. It was located in the body and tail of the pancreas and was removed surgically. Recovery was uneventful and a cure was effected.

Dennis's³ patient was a 40-year-old male who had complained of "rheumatism" of the back, mostly on the right side for a period of three years. At operation, it became apparent that there was a tumor mass originating from the pancreas, probably cystic in nature. Because of the intimate relations of important structures to the mass, extirpation appeared too hazardous and marsupialization was performed. Upon opening the cyst the dermoid contents were noted. "Because of the nature of their lining," Dennis states, "dermoid cysts yield notoriously unsatisfactory results following simple drainage. Had the real character of this one been known it would perhaps have been wiser to accept the additional risk involved in extirpation without opening it, though this would certainly have been great."

The case reported herewith presented symptoms even more vague than the above. Of particular interest also is the fact that this tumor occurred in an infant only two years of age.



FIG 1—Showing the gross appearance of the tumor removed *Diagnosis* Dermoid cyst of pancreas

Case Report—A two-year-old female infant was brought to the DeCourcy Clinic in an acutely ill state. She was emaciated, apparently from malnutrition. Her history revealed that the child had been vomiting intermittently over a period of several months. This symptom had become more frequent within the last two weeks. On examination, she was underweight and undernourished. Her tongue had a furred appearance. There was an odor of acetone on her breath. Pulse was rapid, temperature subnormal. She was sent to the Good Samaritan Hospital, where glucose was administered intravenously upon admission, and several blood transfusions were performed.

She responded well to this treatment and, after 24 hours, was able to retain food. Within a week she had gained two pounds. Consequently, we were inclined, at that time, to attribute her vomiting to the acidosis.

Physical Examination—Palpation of the abdomen revealed a hard nodular mass about the size of a small orange. Two-thirds of the tumor was felt above and one-third below the umbilicus, at the midline. It was freely movable and not particularly tender to touch. Roentgenograms of the stomach and colon, after barium enema, localized the mass as posterior to these structures, in all probability in the lesser peritoneal cavity. This was as definite a roentgenologic diagnosis as could be made.

As the child continued to improve clinically, it was decided to delay surgery until her weight and blood chemistry had reached normal levels. After several weeks, when her general condition was deemed sufficiently good for surgery, operation was performed.

Operation—Under open ether anesthesia, a right rectus incision was made just external to the midline. Upon incision of the gastrocolic omentum, a hard tumor mass was discovered embedded in the pancreas at the middle portion. The mass was removed with ease. Contrary to our expectation, bleeding was scant. There was, however, some oozing which could not be controlled with hot moist pads.

Our problem was what to do for the large denuded area of pancreas remaining. After some thought, an opening was made in the transverse mesocolon and a large strip of omentum was brought through and sutured to the raw surface in the pancreas with No. 00 catgut. A small rubber tube was inserted below this and brought out through the slit in the gastrocolic omentum. Upon completion of the operation, a small blood transfusion was given.

There was a slight amount of drainage from the tube. It was possible, however, to remove the tube on the eleventh postoperative day. The child improved, and convalescence was smooth and uneventful.

Pathologic Examination—*Gross*. Upon opening the tumor, it was found to be a cyst wall containing all the elements comprising a dermoid cyst.

SUMMARY

(1) To date, only two cases of dermoid cyst of the pancreas have been reported.

(2) An additional instance of dermoid cyst of the pancreas occurring in an infant two years of age is described.

(3) Obscurity of symptoms and difficulty of diagnosis are again emphasized.

(4) Satisfactory surgical procedure and treatment are described.

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SPONTANEOUS RUPTURE OF LIVER COMPLICATING PREGNANCY

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SPONTANEOUS RUPTURE OF THE LIVER resulting from insignificant or no trauma has been noted in the literature for more than a century. The first known case was reported by Vesalius at some undetermined date. Andral, in 1829, sketchily reported two cases complicating lesions which may have been gummata or carcinomata. In many of the earliest cases there is some possibility that gastric hemorrhage, secondary to liver disease, may have been mistaken for actual rupture of the liver. Thus, a case quoted in *Paris Medical*, in 1847, by Fauconneau and Dufresne, as reported by Latour, was undoubtedly such an instance.

Abercrombie, as communicated by James Copeland, reported a case of ruptured liver complicating pregnancy in 1844. In this delightfully naive and meticulously detailed report, Abercrombie described a 35-year-old woman who, to obtain relief from "gastrodynia," took recourse to placing a silk handkerchief around her body and pulling it tight to give her relief. On this occasion a servant pulled the handkerchief so tightly that "it made me fear some injury under existing circumstances." Labor followed and normal delivery occurred, followed by collapse some 50 minutes later. The crude stimulants of the time were administered, several famous physicians and surgeons were called in consultation, but the patient died 26 hours after delivery. Autopsy revealed about two pounds of blood in the abdomen and two lacerated openings in the liver substance, about an inch apart. The liver itself presented a mottled appearance throughout and was unusually soft. Bleeding came from a torn branch of the "vena portae."

Devic and Bertel, in 1906, reviewed the literature of spontaneous rupture of the liver. McEwan and McEwan, and Corriden have added more recent and excellent reviews.

Spontaneous rupture of the liver is rare and exceptional. A number of causes for its occurrence have been described. Traumatic rupture we know to be no rarity. Alessandri (1927) stated "Very exceptionally lesions of the liver are observed as the result of violent muscular exertion, as in the course of parturition or epileptic seizures. In such cases it is usually necessary to assume a diminished resistance of the organ as a necessary condition." Our case, although complicating pregnancy, was not in labor.

Causes other than violent muscular effort are multiple (Table I). From this table it can easily be seen that some associated disease or even minor trauma was present in all but three cases of 28 collected. It is no wonder that Sciacca came to the conclusion that when rupture of the liver occurs with minimal cause, the parenchyma is probably not normal.

RUPTURE OF LIVER

TABLE I

CAUSES OF RUPTURE OF THE LIVER OTHER THAN VIOLENT MUSCULAR EFFORT

Date	Author	Age	Cases	Operation	Cause	Result
1829	Andral		2	Autopsy	Carcinoma or gumma	Died
1831	Honore		1	Autopsy	Multiple cavities	Died
1836	Gerard	52	1	Autopsy	None	Died
1844	Sacquepec	44	1	Autopsy	Syphilis	Died
1847	Fauconneau and Dufresne		1	Autopsy	Typhoid fever	Died
1849	Abercrombir	35	1	Autopsy	Pregnancy	Died
1864	Heinzelman		2	Autopsy	Tuberculous peritonitis	Died
1884	Chiari	40	1	Autopsy	Cancer (stomach)	Died
1886	Heinzelman	18	1	Autopsy	Pneumonia	Died
1890	Laurencon	16	1	Autopsy	Syphilis	Died
1892	Pauly	47	1	Autopsy	Biliary colic	Died
1892	Poljakoff		1	Autopsy	Epilepsy	Died
1898	Bar and Keim	Newborn	2	Autopsy	Newborn syphilitic	Died
1899	Carnabel	26	1	Autopsy	Osteotitis	Died
1902	Bernard	62	1	Autopsy	Hemoplegia	Died
1905	Nauwerck		1	Unknown	Common duct stone	Unknown
1906	Devic and Beriel	41	1	Autopsy	Syphilis	Died
1921	Walz		1	Autopsy	Aneurysms	Died
1932	Richon and Cachin	34	1	Operation	Exercise and cough	Recovered
1933	Mast and Streamer		1	Autopsy	Pneumonia and primary carcinoma of liver	Died
1934	Robin	28	1	Operation	Trauma	Recovered
1936	Bradley and Garrett	3	1	Operation	None	Recovered
1937	Sciacca		1	Autopsy	Toxic infection	Died
1938	McEwan	8	1	Operation	Malaria	Died
1940	Corriden	9	1	Operation	Slight trauma	Recovered

Recovery from spontaneous rupture of the liver is rare. First of all, only five cases were diagnosed before death, and while four of these recovered with operation, yet only four recovered of 28 reported cases, all within recent years. More accurate diagnosis, more rapid recognition of the acute surgical emergency present, and more adequate means to replace the blood lost, either by transfusions or by autotransfusion (which is not to be recommended due to the possible contamination and sepsis of liver blood), account for the relatively low operative mortality in the five operative cases. Mortality of traumatic rupture varies from 45 to 78 per cent by comparison. Prompt recognition and early operation with adequate blood replacement are obviously the factors most concerned in recovery.

Pathology of rupture of the liver varies with the accompanying lesion of the liver. Thus, a gumma or carcinoma may easily erode into a blood vessel causing a discharge of blood into the liver parenchyma. Again an aneurysm or hemangioma may rupture and bring about a similar result. A vessel may rupture by reason of arteriosclerosis, as was possibly the case in Bernard's patient. A vessel may become occluded with resultant infarct—then ruptured vessels, as Mazel has suggested. In our case, the rapidly rising blood pressure with toxemia of pregnancy caused rupture of a blood vessel.

Devic and Beriel and, later, Mazel have formulated this theory of the pathology of spontaneous rupture of the liver. "In traumatic rupture, the rupture is the cause of hemorrhage. In spontaneous rupture, the hemorrhage is the cause of rupture. The chain of events leading to the rupture are infarct, hypervascularization at the periphery, rupture of a vessel, intra-

hepatic hemorrhage with resulting rupture of the tissue and production of a subcapsular hematoma which, when rupturing the capsule permits escape of blood into the peritoneum leading to peritonitis and death."

Ruptured liver in the newborn presents a different problem than that with which we are concerned. Its literature, theories and occurrence have been thoroughly reviewed in an article by Silver, in 1938.

We have thus been able to collect but 29 cases (the case of Vesalius included) of true spontaneous rupture of the liver. One of these complicated pregnancies has come to operation and four recovered. Only one other case could be theoretically associated with high blood pressure as a possible apoplexy—the case of Bernard.

Case Report—R. H., white female age 32, was admitted to the Peninsula General Hospital, referred by Dr. Harry S. Kuhlman of Sharptown, Md. The patient was in the early 8th month of her pregnancy. There had been no abnormality in the pregnancy until two weeks before admission when Doctor Kuhlman found her blood pressure increased to 160/110 and first found some albumin in her urine. He sent her home to stay in bed and placed her on a very strict diet, limiting proteins, salt and fluid intake. Despite this care her blood pressure continued to rise, until, on the afternoon previous to admission it had reached the alarming level of 260/160. Her physician advised hospital care that afternoon. At 6 p.m. she vomited once and was transferred to the hospital. No labor pains had occurred.

When next seen by Doctor Kuhlman at the hospital, she was in obvious collapse. Blood pressure 60/0, pulse faintly discernible at 160. She stated that she had some dull ache in the right upper quadrant soon after vomiting but no sharp pain anywhere. Labor had not commenced. No fetal movement had been felt since the attack of vomiting. There was no history of trauma of any kind. A surgical consultation was immediately requested and she was seen by the author a few minutes later.

Physical Examination—The patient was obviously in severe shock, pallid with grey lips, quiet but very nervous, air hunger and feebly perceptible pulse and blood pressure as above described. Fetal heart sounds were absent. *Clinical Diagnosis* Ruptured uterus.

Operation—May 10, 1942. Dr. L. A. Rademaker, and Dr. Robert Starr. Under cyclopropane anesthesia, the abdomen was entered through a lower, midline incision. An incision was made in the lower portion of the uterus and the fetus delivered. There seemed to be an opening in the uterus and therefore, a Porro excision of the uterus, tubes and ovaries was done at the supravaginal level. The ligaments and blood vessels were sutured. It then became obvious that excessive hemorrhage was still occurring from some place in the upper abdomen and the tear and damage of the liver were found. Two long packs were placed in the damaged portion of the liver protected by tissue drape in the intra-abdominal part. The patient at this time was in desperate condition and a blood transfusion was administered. The ligaments were tied to the cervical stump but because of the patient's condition no attempt was made to peritonealize. Then the wound was quickly closed in layers about the drains, using chromic catgut in the peritoneum and muscle, stainless steel wire in the fascia, plain catgut in the fat and clips in the skin. The patient left the operating room in poor condition.

Surgical Pathology—The uterus contained a small, immature dead female fetus. The abdomen was filled with blood. There were multiple fibroid tumors of the uterus itself. The right lobe of the liver contained a vertical tear six inches in length, with an area of degenerated tissue which appeared to be mush, and about the size of a grapefruit.

Postoperative Course—The patient had a very stormy convalescence, blood transfusions were given on May, 11th, 12th and 13th. Syntamin, blood plasma and glucose were added. Due to pressure of the pack against the diaphragm she developed a pleural effusion, and 600 cc of bloody, serous fluid were removed by aspiration on May 25, 1942, and repeated daily until May 29, 1942, when but 40 cc could be obtained.

The pack was removed May 19, 1942 under gas anesthesia in bed, and was followed by a profuse drainage of material so closely resembling blood that the resident became alarmed and repacked the incision. This pack was removed May 24, 1942, and was followed by further drainage of serous bloody material which smelled like biliary drainage but did not appear bile-stained. An abscess of the left breast further complicated recovery—necessitating incision and drainage, under local anesthesia, on June 5, 1942.

Each of these complications produced its storm in temperature, pulse and respiration. Sulfanilamide preparations did much to abate each storm as it occurred. At times the patient's condition seemed entirely hopeless, but she gradually improved after the last complication was conquered and was discharged July 4, 1942, 57 days since admission. Her chest was clear, the breast had completely healed, her abdominal wound was still draining slightly. Her blood count on June 1, 1942 showed Hb 66, RBC 3,510,000, WBC 12,250. Her blood pressure on discharge was 165/100, and the urine showed a slight trace of albumin, with specific gravity of 1.011.

Follow-Up—August 10, 1942. The patient appeared to be quite healthy, with a well-healed solid abdominal scar. She was taking stilbestrol, 0.1 mg per day, which controlled her hot flushes very well. She was able to work and felt as strong as ever. Her blood pressure was 145/90.

This, as far as we can discover, is the fifth reported case of recovery from a spontaneous rupture of the liver, and the second case of spontaneous rupture of the liver complicating pregnancy. The high blood pressure occurring in a short period of time suggests the cause for apoplexy—especially when a vomiting attack immediately preceded collapse.

Several significant facts appeared:

(1) Careful observation by the family physician made it possible to operate; otherwise, the patient would have died within a few hours, and the diagnosis, if made at all, would have been made at autopsy, as in the majority of reported cases of spontaneous rupture of the liver.

(2) The Porro procedure was the quickest means of removal of the fetus and the uterus to prevent any further bleeding from that source.

(3) Death of fetus as result of hemorrhage of the mother.

(4) Pleural effusion from pressure of the pack on diaphragm.

(5) Prompt multiple blood and plasma transfusions are necessary to save these desperately ill patients.

One is led to speculate if some of those cases of death by collapse during treatment for eclampsia may not be due to undiagnosed rupture of the liver.

SUMMARY

We have reviewed the literature of spontaneous rupture of the liver finding but four other cases of recovery and but one other report complicating pregnancy. We have reported such a case of spontaneous rupture of the liver complicating pregnancy and following a rapidly developed hypertension.

This case was operated upon while in desperate condition, under a mistaken diagnosis as to source of hemorrhage. The diagnosis of internal hemorrhage was made early enough so that recovery could occur with the modern methods to combat shock and hemorrhage. Recovery was complicated by pleural effusion, secondary hemorrhage, breast abscess, but final complete recovery ensued.

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LIVER NECROSIS IN BURNS

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BARDLEN (1898) described "focal degeneration in the lymphatic tissues liver and advanced parenchymatous degeneration of the kidneys" in autopsies upon five children with extensive burns Weiskotten (1919) found focal necrosis of the liver in two of ten burn autopsies Pack (1926), after a comprehensive review of the subject, stated that "there are no internal or visceral lesions pathognomonic of burns and scalds" Wilson (1935) attributed severe necrotic or fatty degeneration of the cells at the center of the liver lobule to the acute toxemia following severe burns A further study of 33 cases by Wilson MacGiegor and Stewart (1938), compared the liver lesion in burns to acute yellow atrophy

McClure (1939) and McClure and Lam (1940) reported marked jaundice in clinical cases with marked central necrosis of the liver in a case which failed to survive Belt (1939) compared the midzonal necrosis of the liver found in four fatal burn cases to the liver lesions of yellow fever because of the demonstrated Councilman bodies and intranuclear inclusions Wells (1940) was probably the first to offer objective data, suggesting that the tannic acid treatment might be the cause of liver necrosis, when he reproduced the lesion in rabbits by intraperitoneal and subcutaneous injections of tannic acid

As a part of a study on burns projected by the National Research Council,* and carried out at the Henry Ford Hospital, further experimental study of liver damage was undertaken in an effort to determine

- 1 The effect of the burn alone on the liver
- 2 The effect of various types of protein coagulating chemicals, including tannic acid on the liver
- 3 The effect of burns treated with protein coagulating chemicals on the liver
- 4 The effect of tannates on the liver and the significance of their identification in the urine of tannic acid treated and injected animals

EXPERIMENTAL STUDIES

The experiments were all performed upon dogs under morphine and ether, or morphine and chloroform anesthesia Morphine was continued for 24 to 48 hours after the procedures routinely, and longer if needed for the

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the Henry Ford Hospital

Permission to publish this paper has been granted by the Committee of Medical Research of the Office of Scientific Research and Development

FIG 1

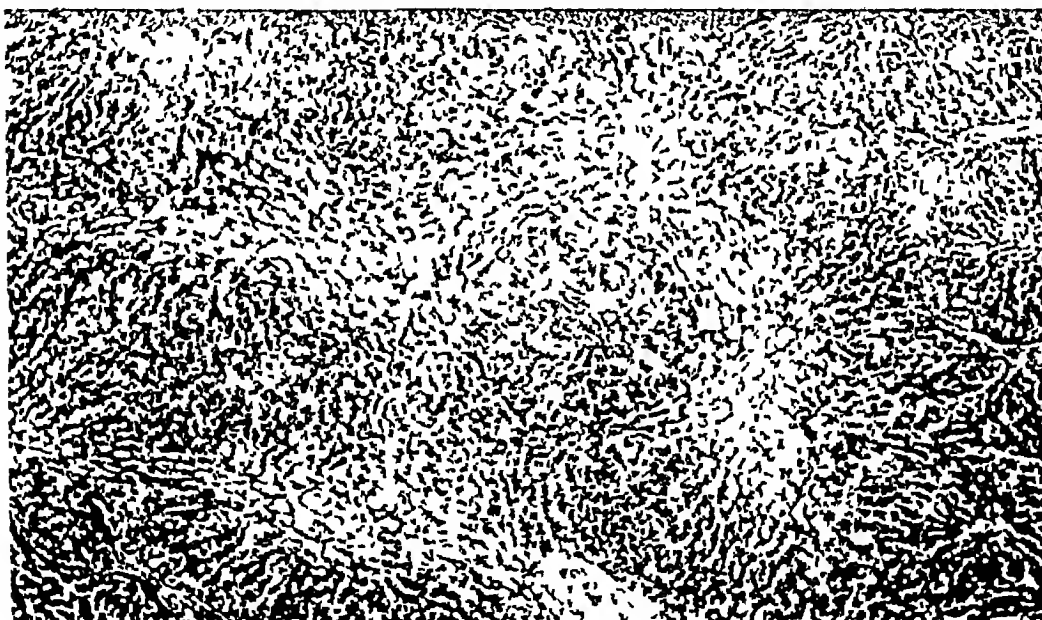
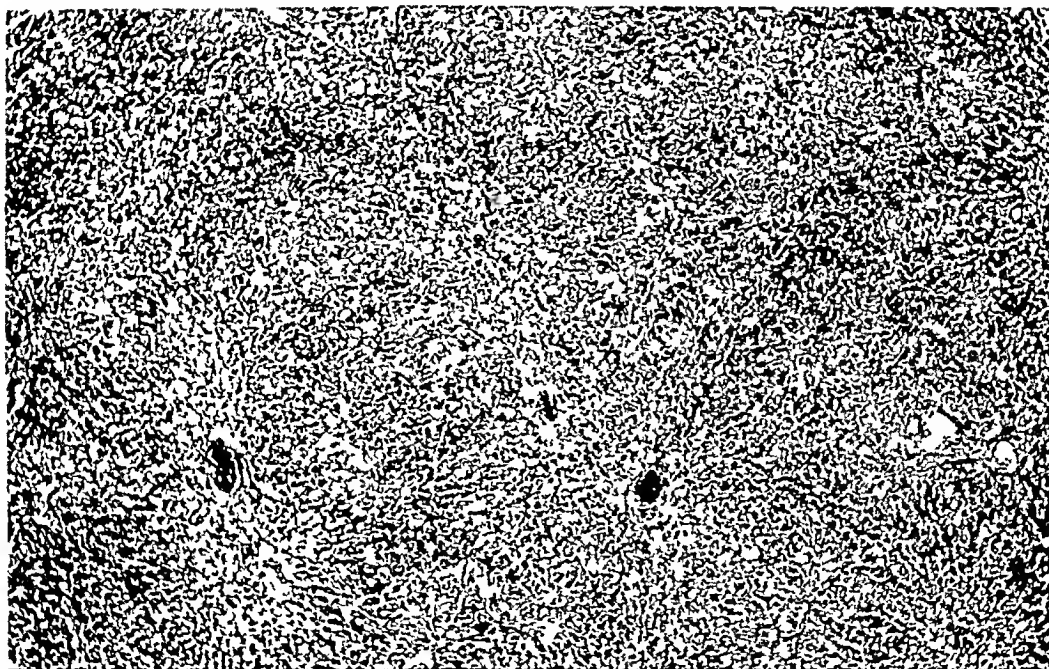


FIG 2

FIG 1—Dog No. 3118 Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with sterile vaseline. Survival—10 days. Shows marked congestion, myelinization and necrosis at the center of the liver lobules. (Low power)

FIG 2—Dog No. 3121 Photomicrograph of liver from animal in which a 60% skin burn was produced with Bunsen burner and dressed with vaseline scarlet R. Survival—9 days. Shows spotty necrosis about the center of the lobules with intense engorgement. (Low power)

comfort of the animals. In case chloroform was used care was taken not to prolong the administration more than 15 to 20 minutes. The burns were produced with both dry heat and moist heat over 60 to 65 per cent of the body surface and were uniformly of third-degree severity.

GROUP 1—To determine the effect of burns alone on the liver the lesion was immediately dressed with neutral substances sterile vaselined gauze

in 12 instances, lanolin in two instances, and normal salt solution in two instances

In this group, 16 animals with large skin burns were used. The duration of life following the burn ranged from 4 to 20 days. The dressings, following the Koch method, were changed infrequently, if at all. The injured skin underwent maceration in 4 to 5 days and usually was the site of infection and suppuration. At autopsy, emaciation and anemia along with local and general infection were the usual findings. Grossly, the liver was enlarged, and in those living shorter periods, congested. The spleen was usually enlarged to 2 to 4 times the normal. Metastatic abscesses, with or without hemorrhages, were frequently seen. Curling's ulcers of the duodenum were produced in 5, or 33 per cent, of this group, and will be discussed in a later communication. Microscopically, the liver lesions ranged from marked suggestion of the sinusoids, with compression of the liver cords, to varying amounts of granular, vacuolar and fatty degeneration in experiments running 4 to 10 days, while myelinization and central necrosis was seen in those surviving 8 to 10 days (Figs 1 and 2). The central necrosis in this series is a late development and associated with intense infiltration of the affected area. Although such lesions were accompanied by depression of liver function and icterus indices up to 20, the picture was not that of acute liver insufficiency.

GROUP 2—To determine the effect of protein coagulating chemicals on the liver these substances were injected intraperitoneally and subcutaneously, and applied as a dressing to large surfaces from which the skin had been excised in 112 animals.

A Silver Nitrate—In this group, 15 animals were used, and all were injected subcutaneously with 2 per cent solution while the animals were under morphine and ether anesthesia. After injection morphine sulphate was given as indicated.

These animals survived the injection from 1 to 23 days. One animal died from distemper. Four animals lived only one day, but in all these marked, acute congestion of the liver, especially about the center of the lobule, was noted. Granular degeneration and early necrosis was seen in three. Two showed central necrosis of the liver of marked degree and extensive myelinization. Thus 5 or 33.3 per cent, showed necrosis in varying degree but only 2 or 13.3 per cent, had extensive necrosis and myelinization, and these died on the eighth and eighteenth day, respectively. Eleven of the 15 died from the effects of the injection, and 4 were sacrificed because of ulceration (Figs 3 and 4).

B Alum—Nine animals were used for the subcutaneous injection of aluminum and potassium sulphate. The 10 per cent solution was sterile and used in amounts ranging from 60 to 180 cc. The injections were all done under morphine and ether anesthesia. The length of life after injection ranged from 3 to 10 days, but five animals were sacrificed because of

ulceration and infection. Microscopically, the livers showed marked congestion and engorgement, with granular, and especially vacuolar degeneration. These degenerative changes obscure the cells near the center of the lobule but do not represent necrosis of cells such as seen in other groups.

C Sulphosalicylic Acid —Only six animals were used in this group, partly

FIG 3

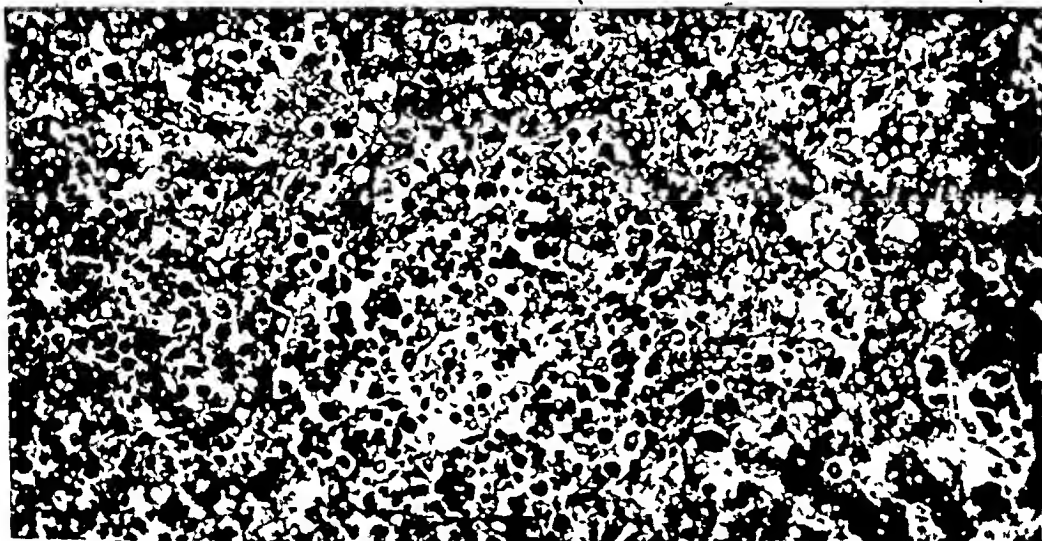


FIG 4

FIG 3—Dog No 3126 Photomicrograph of liver from animal receiving 120 cc silver nitrate 2% subcutaneously. Survival—5 days. Shows marked congestion, hemorrhage, and beginning necrosis at the center of the liver lobules. (Low power.)

FIG 4—Dog No 3041 Photomicrograph of liver from animal receiving 100 cc 2% silver nitrate subcutaneously. Survival—18 days. Shows central necrosis of liver lobule with intense myelinization. (Medium power.)

because the pathologic changes in the liver and other organs were minimal and partly because the sites of injection opened spontaneously and drained. Even the animals receiving from 120 to 140 cc of 3 per cent solution, and surviving 7 to 10 days, showed congestion with early necrosis in two, and myelinization in one animal.

D Zinc Peroxide—In this group only five animals have been used to date. All were given subcutaneously suspensions of sterile ZnO_2 in sterile water, in the first instance 200 cc of 7 per cent, and the other four 110 cc of 22 per cent. These animals survived from 6 to 15 days. Three showed clinical jaundice with icterus indices from 15 to 35. Two showed central necrosis, while all showed congestion coupled with granular and vacuolar degeneration. The jaundice seen in this group is out of proportion to the necrosis seen in the liver but corresponds with the rapid weight loss and short duration of life.

E Ferric Chloride—Ferric chloride is one of the chemicals used as a tanning agent in the treatment of burns, hence it was included in this study both for subcutaneous injection and as a dressing for burned areas.

Thirteen animals were used for subcutaneous injection, 11 receiving from 100 to 175 cc of a sterile 5 per cent solution and two receiving 110 and 120 cc, respectively, of a sterile 10 per cent solution. Ten of the 13 died in from 1 to 5 days, and three were sacrificed after becoming moribund in 2 to 5 days. At autopsy, there was extensive greyish-yellow coagulation necrosis at the site of injection and extending around either side to the abdomen, associated with marked edema and blood extravasation. The hemorrhagic tendency was also seen at times in the pericardium and intestines. The liver was usually enlarged, mottled and dark red in color. Microscopic sections showed marked acute congestion with hemorrhage in seven animals and central necrosis in five, or in 38 per cent. This incidence of necrosis is somewhat higher than with tannic acid but the extent of the necrotic areas tends to be less. Hemorrhage, with and without necrosis is more striking with ferric chloride than with tannic acid (Fig 5).

F Gallic Acid—It has been suggested, from time to time, that gallic acid is toxic for the animal organism at least that it is more toxic than tannic acid. This has been given as a reason for insistence on using only freshly prepared tannic acid solutions in the treatment of burns. Gallic acid, as a sterile 7.5 per cent solution, has been used five times for subcutaneous injection in amounts ranging from 110 to 150 cc. Microscopically the livers of these animals showed principally acute congestion, hemorrhage and compression of the liver cells.

G Quebracho Tannin—Only four animals were used in this series because of the scarcity of material. The material used was the crude tannin* made up in a solution roughly comparable to the 7.5 per cent tannic acid, as far as the tannin content is concerned. This solution was injected subcutaneously in amounts ranging from 90 to 150 cc. The animals survived for periods ranging from 8 to 18 days. Clinical jaundice occurred once and, microscopically, central necrosis of the liver was found in two animals. Although this group is small it suggests that crude quebracho tannin has the same, or greater, possibilities for tannate absorption as tannic acid.

* Furnished by Parke, Davis & Co

FIG 5

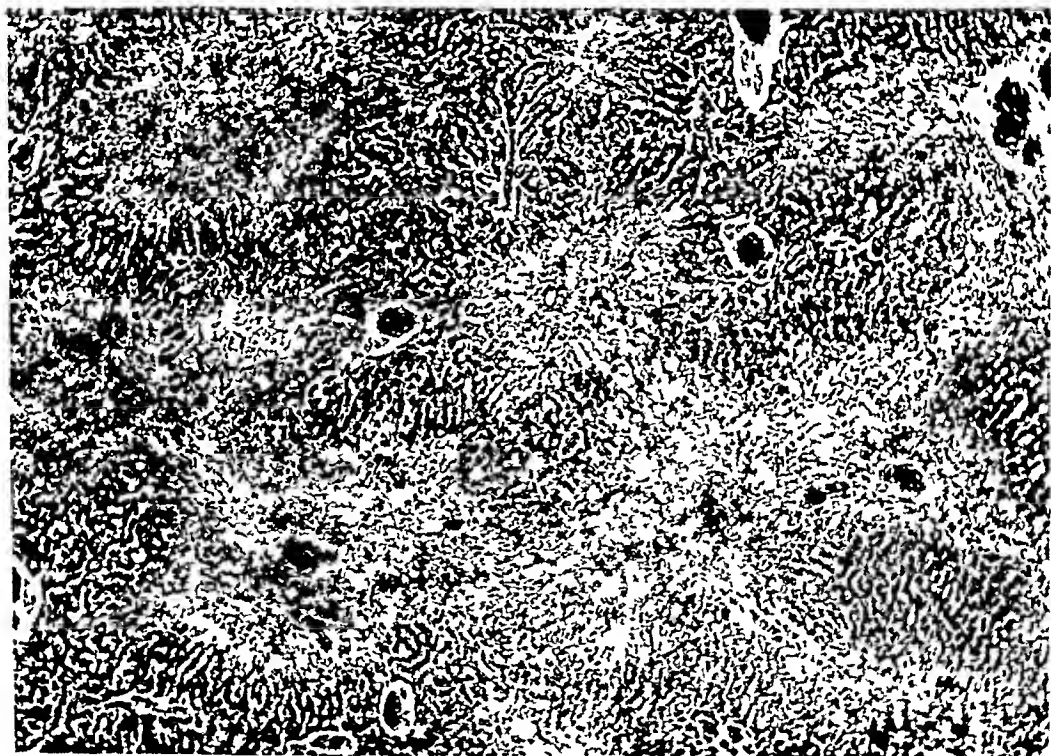
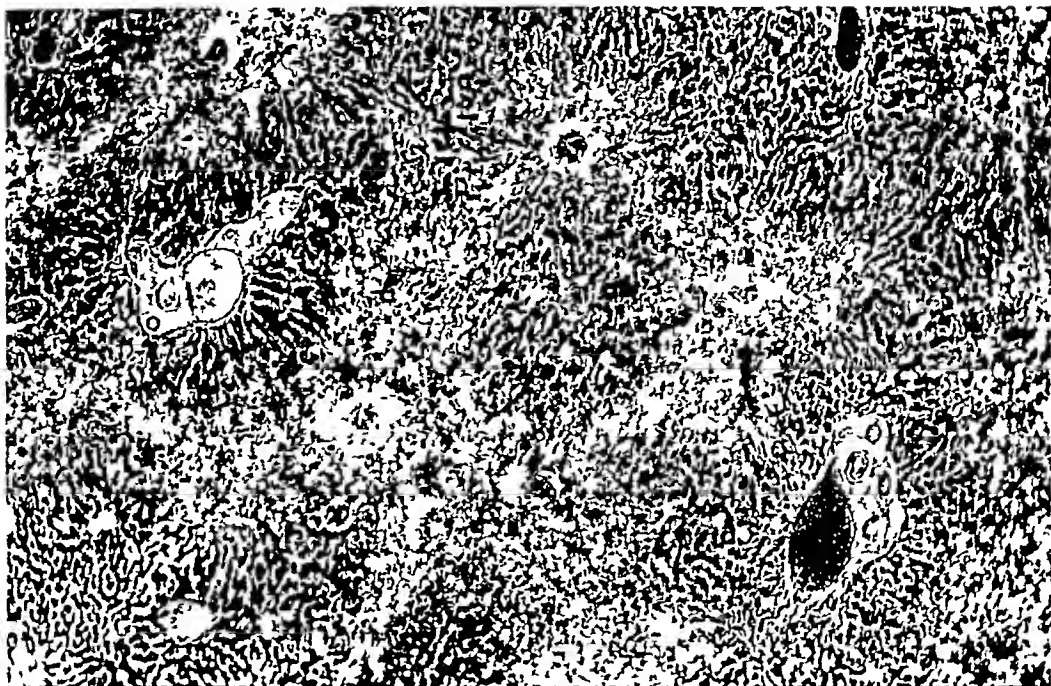


FIG 6

FIG 5—Dog No 3160 Photomicrograph of liver from animal receiving 120 cc of 10% ferrie chloride subcutaneously Survival—3 days Shows extensive necrosis fatty infiltration, and hemorrhage involving approximately one third of the liver tissue (Low power)

FIG 6—Dog No 3124 Photomicrograph of liver from animal receiving 150 cc of 7.5% tannic acid subcutaneously Survival—3 days Shows very extensive central necrosis of liver lobules with hemorrhage (Low power)

H Tannic Acid (used as intraperitoneal and subcutaneous injection) — In this group there are 41 experiments each including the injection of sterile 7.5 per cent tannic acid solution Six intraperitoneal and 33 subcutaneous injections were done The intraperitoneal route was abandoned because of

the violent peritonitis produced and the short duration of life, however, central necrosis of the liver was seen twice, or in 33.3 per cent. With subcutaneous injections the dose ranged from 60 to 200 cc., depending upon the size of the animal. These injections were all done while the animals were under ether anesthesia, and were made at several points. The length of life after injection ranged from 2 to 16 days.

Autopsy showed extensive coagulation necrosis at the sites of injection and extending down the sides around the abdomen, especially with the larger doses. In five instances, 7.5 per cent tannic acid neutralized to pH 7.4 with sodium bicarbonate was used subcutaneously, and the resulting coagulation and edema was comparable to that from the usual tannic acid at pH 3.5.

None of the animals living less than two days showed necrosis of the liver, but marked acute congestion at the center of the lobule associated with granular and vacuolar degeneration predominated. In the 25 animals living 2 to 16 days, central necrosis of the liver was seen six times, or in 25 per cent, and extensive fatty degeneration twice, or in 8 per cent (Figs 6, 7 and 8).

I. Tannic Acid Jelly (as dressing for areas from which skin was excised).—A group of three animals from which skin areas 20 x 20 x 16 inches were excised, had the denuded area dressed with sterile 7.5 per cent tannic acid jelly. These animals lived from 10–16 days. At autopsy, infection and suppuration was present in the wounds. Microscopically, the livers showed congestion, fatty degeneration and myelinization, but no central necrosis.

Analysis of the lesions obtained by the injection of these seven different chemical coagulating agents shows that the three most commonly used in the treatment of burns are the same ones responsible for the liver damage, namely, silver nitrate, ferric chloride and tannic acid.

The liver damage associated with the injection of silver nitrate developed relatively late and was accompanied by intense myelinization. Clinical jaundice and liver insufficiency were not produced with silver nitrate.

The liver damage occurring after the injection of ferric chloride was acute and hemorrhagic. The incidence was 38 per cent as compared with 25 per cent for tannic acid in the dosage-range used. Clinical jaundice was seen only twice in this group.

Central necrosis of the liver occurred in 33.3 per cent of animals receiving intraperitoneal injections of tannic acid and 25 per cent of animals receiving subcutaneous injections. The necrosis of the liver was produced more promptly and was more extensive than with the other coagulating chemicals. Clinical jaundice was seen on the fourth day and was progressive unless measures to combat it were instituted. The jaundice was accompanied by refusal of food, loss of weight and strength, vomiting, bloody stools, and coma.

GROUP 3.—To determine the effect of burns dressed with protein coagu-

lating chemicals on the liver, these chemicals were applied as dry dressings and as wet dressings to large skin burns in 31 animals

A Experiments with Skin Burns Treated with Tannic Acid Prepara-

FIG 7

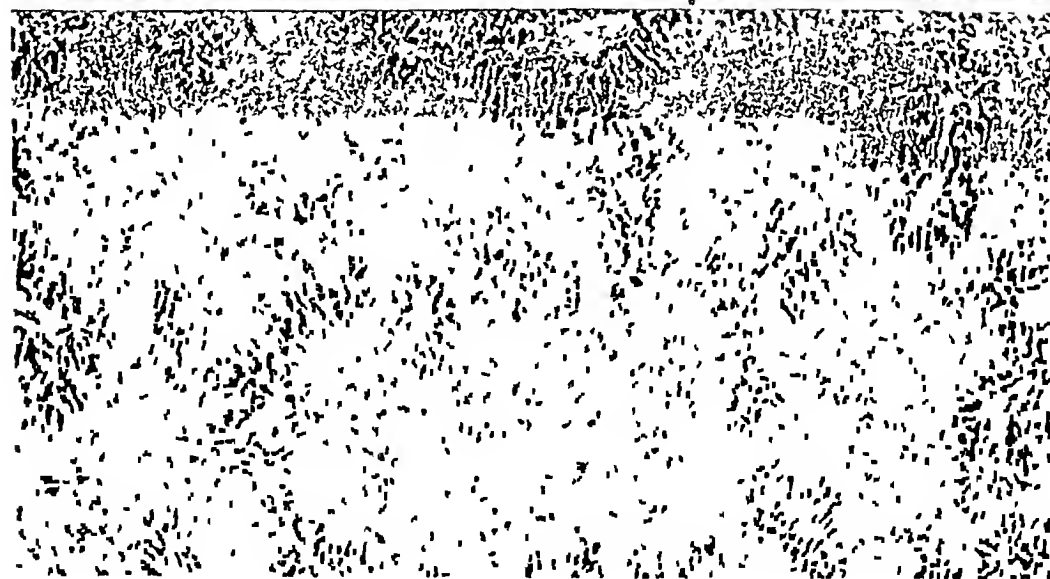
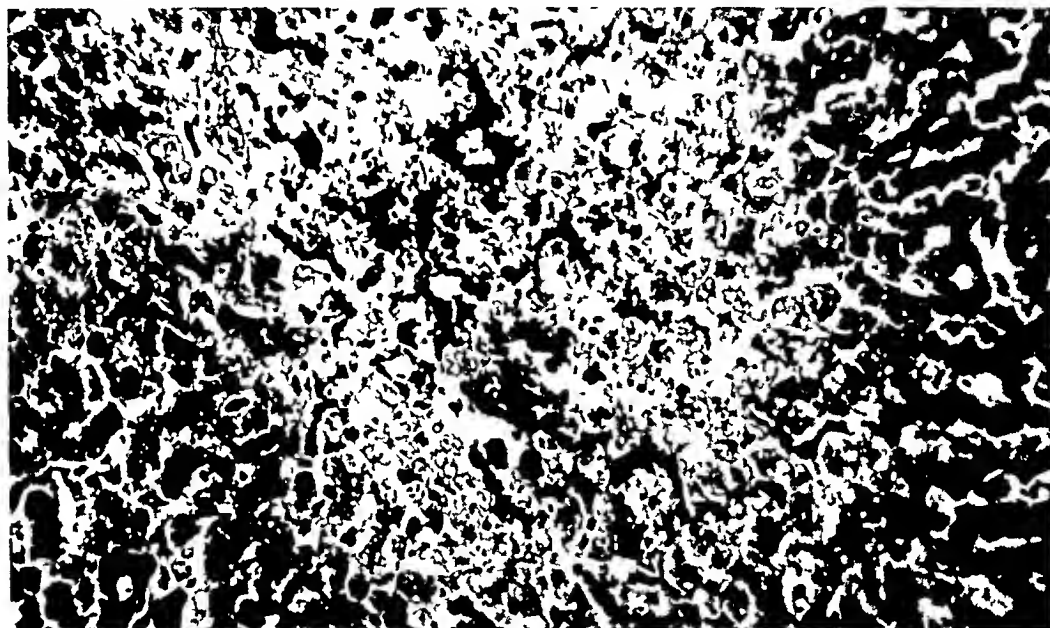


FIG 8

FIG 7—Dog No 3124. Photomicrograph of liver from animal receiving 150 cc of 7.5% tannic acid subcutaneously. Survival—3 days. The large lighter zone at the center shows complete lysis of liver cells with engorgement of the sinusoids and central vein (Medium power)

FIG 8—Dog No 3161. Photomicrograph of liver from animal receiving 150 cc of neutral tannic acid 7.5% subcutaneously. Survival—2 days. Central zone is necrotic the liver cells being represented only by amorphous blue-staining material. The liver cells at the periphery also show degeneration so that they do not stain well (Medium power)

tions—In the group of 24 animals, skin burns covering the entire back and sides were produced ranging from 60 to 65 per cent of the body surface. In ten instances the burns were produced with a Bunsen burner and 14 times with a steam jet. The length of life was from 2 to 27 days. Clinical jaundice with icterus indices ranging from 20 to 58 was seen in three animals.

of 12 per cent, and all these had a wet dressing with the tannic acid preparation. The urine from the animals with wet dressings was unusually dark in color and gave strongly positive tests for tannates.

Autopsy showed third-degree burns and good tanning in all, including those treated with neutral solution, but with the wet dressings the skin was macerated and usually suppurating. There was marked subcutaneous edema, especially over the abdomen, as in Dog No 3170 (Fig 9). Here it was noted that the edema fluid was blackened by the tannic acid, although the animal lived only 24 hours, suggesting that the tannate was absorbed especially when this plasma was reabsorbed. Metastatic abscesses of the kidneys were present in some cases. Central liver necrosis was present twice and central degeneration twice. In only one instance (Dog No 3076) was necrosis associated with a dry dressing and in this instance crude quebracho tannin was used as a spray (Fig 10).

One animal Dog No 3142 with a fire burn, and a wet dressing of plain 75 per cent tannic acid jelly passed blood from the intestinal tract for 24 hours preceding death and was found to have a large Curling's ulcer, with blood clot attached in the first portion of the duodenum.

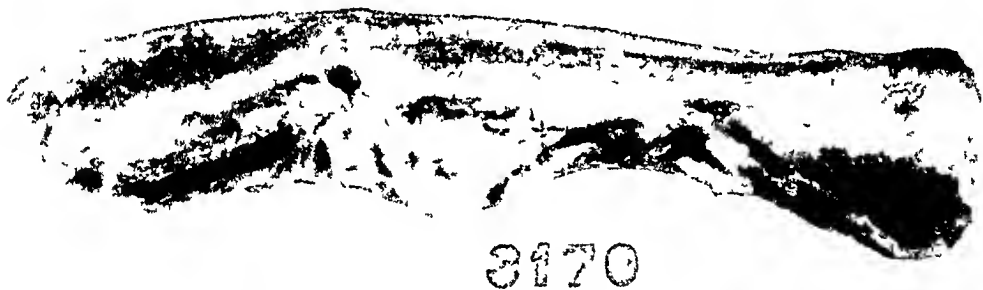


FIG 9—Dog No 3170. Hyd burn produced with steam jet covering 60% of the body surface to which a wet dressing of 75% tannic acid jelly was applied. Survival—1 day. Shows penetration of the tannic acid dressing 1 cm into the edematous subcutaneous tissue beneath the burn.

B Experiments with Skin Burns Treated with 5 per cent Ferric Chloride
In this group 5 per cent sterile ferric chloride solution was used to dress and tan large burned areas of about 60 per cent of the body surface. Two burns so treated were produced with the Bunsen burner and three with the steam jet. This solution produced a good tanning in both types of burns after four to six applications over a 12- to 24-hour period—fully equal to that produced by tannic acid. Three animals had dry dressings and lived from 7 to 16 days before being sacrificed while still in good condition. Two in which wet dressings were applied died after 8 and 11 days, respectively. These two were the only ones in this series showing significant lesions in the liver, Dog No 3141 showing extensive central necrosis with hemorrhage, and Dog No 3145 showing marked fatty infiltration and congestion (Fig 11).

In this group large skin burns were actually treated with tannic acid and ferric chloride preparations. Here conditions similar to those present in the handling of clinical burns were reproduced. Clinical jaundice with icterus

LIVER NECROSIS IN BURNS

FIG 10

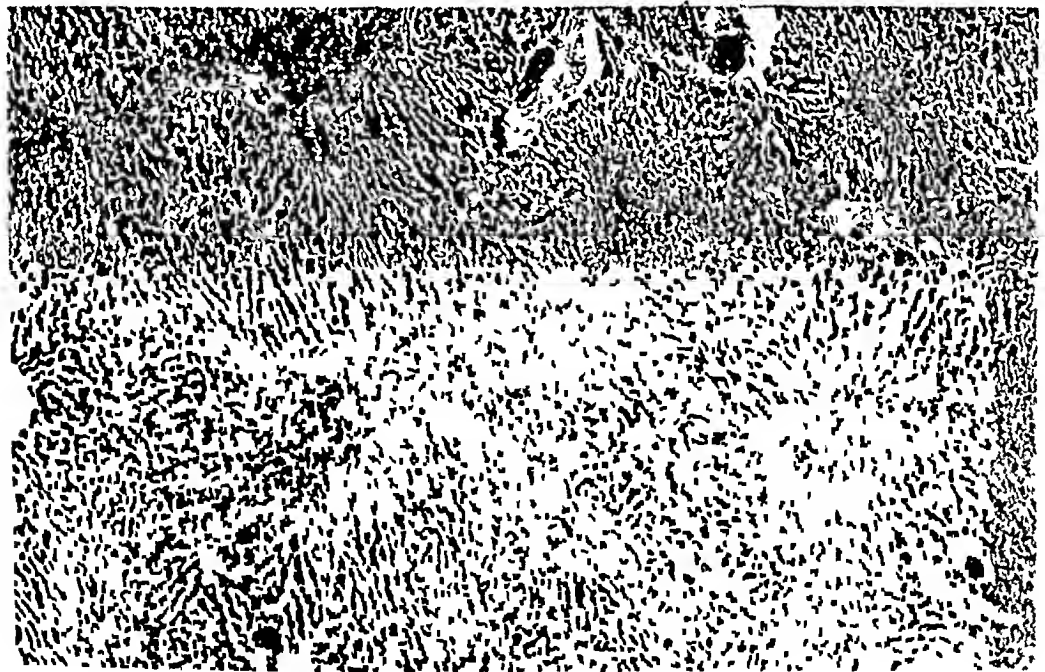
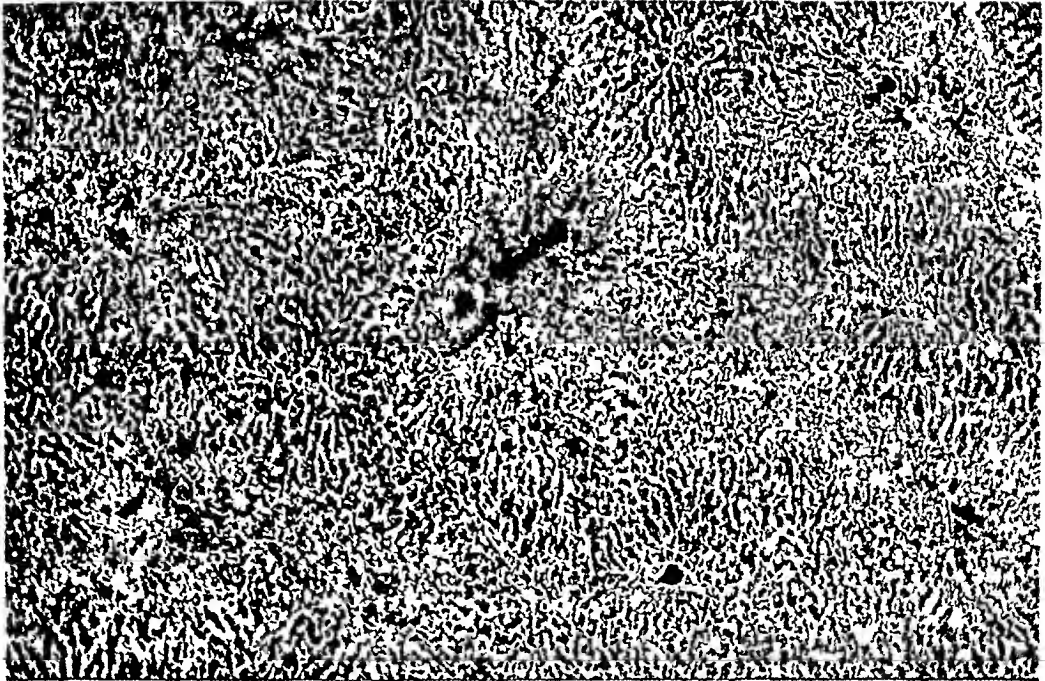


FIG 11

FIG 10—Dog No 3176 Photomicrograph of liver from animal in which a burn was produced with steam jet covering 60% of the body surface, to which a wet dressing of 7.5% tannic acid in cetyl alcohol base was applied. Survival—11 days. Shows marked congestion and hemorrhage with central necrosis. (Low power.)

FIG 11—Dog No 3141 Photomicrograph of liver from animal in which approximately 60% burn was produced with steam jet and dressed with 5% ferric chloride jelly. Kept wet with phofilm covering. Survival—8 days. Shows marked engorgement of blood vessels with necrosis and hemorrhage at the center of the lobule involving approximately 40% of the liver tissue. (Low power.)

indices ranging from 20 to 58 was seen in three animals, or 12 per cent, all of which had wet dressings rather than the usual drytanned eschar. Central necrosis and degeneration was found in four, or 16 per cent. Only one of these had a dry dressing, and that consisted of crude quebracho tannin applied as a spray.

On the basis of these findings, wet dressings and baths of tannic acid will give us the highest incidence of liver necrosis and should be avoided, as pointed out by Davidson in his original contributions

GROUP 4 —To determine the effect of tannates on the liver, blood plasma was precipitated with tannic acid, twice washed and injected subcutaneously. Alkaline sodium tannate solution pH 9 was injected intravenously. Tannates and gallates excreted in the urine were identified.

It had been assumed that tannic acid with a pH of 3 combined with proteins formed an insoluble compound which would be inert in the body. However, such compounds were prepared using blood plasma as the source of protein and the twice washed precipitate was injected subcutaneously in 100 to 120 cc amounts of the 50 per cent suspension. Two of the four animals injected showed early central necrosis of the liver, suggesting at least that the material was absorbed and was toxic for the liver (Fig 12). Following this experiment it was observed that tannic acid was absorbed into the edematous subcutaneous tissues beneath the burned tanned skin for a distance of 1.5 cm, as evidenced by the brownish-black discoloration. Then the dark brownish urine excreted by both the animals injected subcutaneously with tannic acid preparations and those burned and dressed with the same preparations, were shown to contain tannates, as identified by Dr V. Schelling. Neutralized tannic acid and quebracho tannin used for subcutaneous injection and dressings excreted relatively large amounts of tannates and gallates.

Detection of Tannates in Urine —Tannates excreted in urine are demonstrated by the bluish-black color with ferric chloride. Since however, gallic acid, a hydrolysis product of tannic acid, gives the same color, a more specific reagent is required. Samin's reagent (Meick's Index, 5th edition, p 808) fulfills this requirement. It gives a white precipitate with tannic acid but no precipitate with gallic acid.

Some urines which gave a positive ferric chloride reaction did not precipitate with Samin's reagent indicating that gallates were present in these urines. The kidney according to Sieburg and Mordhorst, does not possess an enzyme system that is capable of splitting tannins. However, the liver, according to these authors, might be the site where splitting of tannins occurs.

Attempts were made to use Folin and Denis phenol reagent for a more quantitative evaluation of tannates in urine. All urines which gave a positive ferric chloride reaction developed a blue color with this reagent after treatment with silver-lactate- $NaCl-HCl$. However, the color developed was different for each urine and could not be matched adequately with the color of the standard prepared from tannic acid.

Although neutralized tannic acid proved quite effective in the coagulation of proteins, both *in vitro* and *in vivo*, alkaline sodium tannates with pH 9 failed to coagulate proteins so that it became possible to inject such solutions directly into the blood stream of both rabbits and dogs without immediate

of delayed reaction Two dogs of 7 and 8 kilos were given 15 cc of 7 per cent sodium tannate solution intravenously These animals excreted brownish urine containing tannates, and showed a rapidly deepening jaundice at the end of 48 hours One animal died in 48 hours in deep coma, with

FIG 12

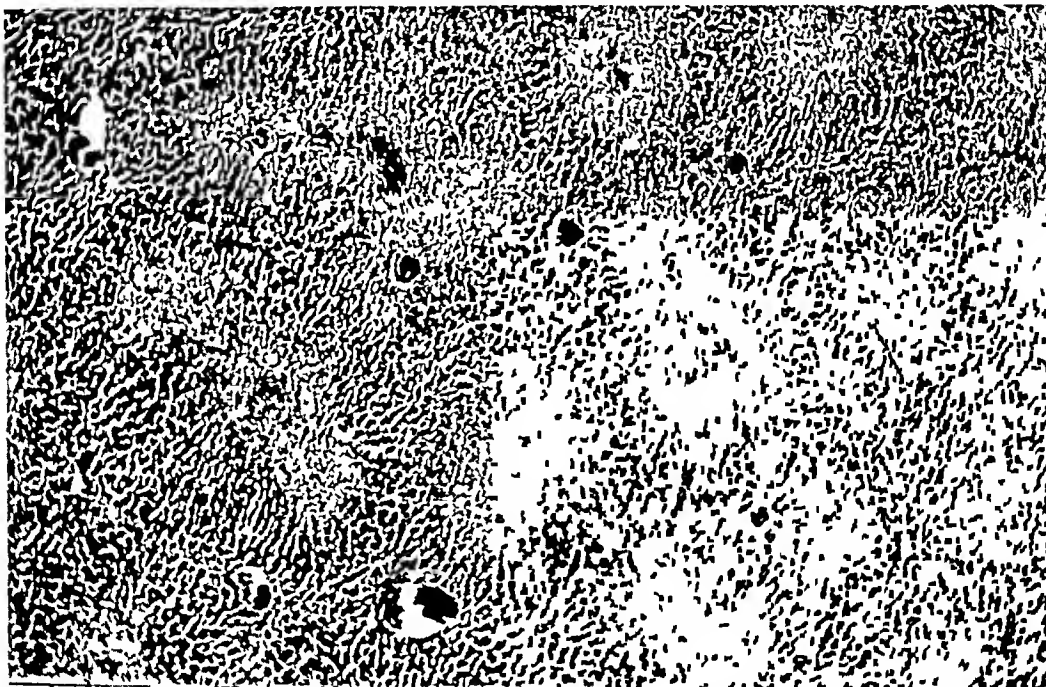


FIG 13

FIG 12—Dog No 3137 Photomicrograph of liver from animal receiving 100 cc of twice washed protein tannate subcutaneously Survival—3 days Shows extensive central necrosis of liver lobule (Low power)

FIG 13—Dog No 3193 Photomicrograph of liver from animal receiving 15 cc of 7% sodium tannate solution intravenously Survival—3 days Clinical jaundice marked Icterus index 140 Shows vacuolar degeneration and necrosis of liver cells about the centers of lobules (Low power)

an icterus index of 140 (Fig 13) The second lived a week, with increasing jaundice, marked listlessness, and refusal of food Autopsy of these animals showed a small, brownish-green liver that was flabby and soft and friable

on section. The usual lobulation could not be made out. Microscopically, there was acute central necrosis of 50 per cent of the liver tissue.

Rabbits of 3 and 4 kilos were given 8 cc of the 7 per cent sodium tannate solution into the marginal ear vein. No jaundice was detected either clinically or at autopsy, but all succumbed in two to six days. Microscopically, the livers showed more marked central necrosis than those of the dogs receiving this solution. Only a fringe of liver cells remained at the periphery of the lobule while the centers were necrotic and hemorrhagic (Fig. 14).

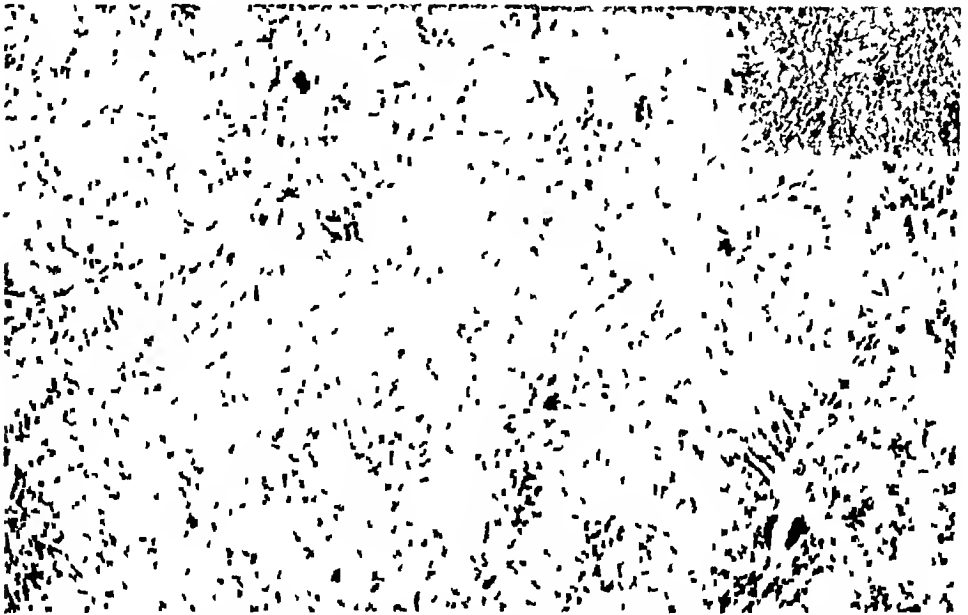


FIG. 14.—Rabbit No. 3195. Photomicrograph of liver from animal receiving 7 cc of 7% sodium tannate solution intravenously. Survival—24 hours. Shows complete lysis of the cells of the liver lobule with the exception of a fringe about the periphery. (Low power.)

The production of liver necrosis by the subcutaneous injection of washed tannates and the intravenous injection of alkaline sodium tannate solutions demonstrates the etiologic importance of tannates in the pathogenesis of this lesion. Further the identification of relatively large amounts of tannates and gallates in the urine excreted by animals burned and treated with tannic acid preparations, as well as in the urine of those injected with tannic acid subcutaneously, shows that these tannates are absorbed from the site of treatment or injection into the blood stream. This fact being established, it is clear that the liver cells may be destroyed just as they are when tannates are injected intravenously.

SUMMARY AND CONCLUSIONS

1. Large experimental burns result in marked engorgement of the sinusoids of the liver, especially about the central veins, and compression of the liver cells in this area.

2. Acute compression of the liver cords is followed even in the groups treated with sterile vaseline and sterile salt solution by granular, vacuolar

and fatty degeneration. With longer survival, especially if infection either in the form of pneumonia or suppuration of the burned area occurs, actual necrosis of liver cells at the center of the lobule, with myelinization, may be seen.

3 Introduction of any of the coagulating agents mentioned, either as a dressing for a burned or denuded area, or as a subcutaneous injection, increased the incidence of degeneration and necrosis of liver cells, with or without hemorrhage.

4 Oddly enough the three coagulating agents that have been used in the treatment of burns are the only ones that have, in this work, increased the danger of clinical jaundice and liver insufficiency. These chemical agents are in order of importance: Tannic acid, ferric chloride and silver nitrate.

5 Tannic acid used as a wet dressing for burns has produced clinical jaundice in the dog in 12 per cent and central necrosis of the liver in 16.5 per cent. In only one instance was liver necrosis seen associated with the dry tanning of a burn, and in this crude quebracho tannin was used.

6 Tannic acid used as a subcutaneous injection in a series of 25 animals has produced liver necrosis in 25 per cent. With intraperitoneal injection, in a series of six, liver necrosis was produced in two, or 33.3 per cent.

7 Quebracho tannin and tannic acid neutralized with sodium bicarbonate in a small series were more potent than tannic acid in the production of liver damage.

8 Animals having burns treated with wet dressings of tannic acid or tanning preparations and those receiving subcutaneous injections of these preparations excrete relatively large amounts of tannates and gallates in the urine. These groups have the highest incidence of liver necrosis.

9 Sodium tannate of pH 9 does not coagulate protein readily and may be given in amounts of 10 to 20 cc. of the 7 per cent solution daily without reaction. Such injections in four rabbits and five dogs have resulted in the consistent production of liver necrosis in both groups with clinical jaundice and death in the dogs.

10 The excretion of tannates in the urine of animals receiving wet dressings or injections of tannic acid, coupled with the fact that these animals along with those receiving tannates intravenously have a high incidence of jaundice and liver necrosis, shows the etiologic relation of these tannates to the liver lesions.

11 Silver nitrate used in 2 to 10 per cent sterile aqueous solution subcutaneously, produces extensive necrosis and edema at the site of injection, with some degeneration, hemorrhage, and necrosis of the liver. However, clinical jaundice has not occurred, and death could not be charged to the grades of liver damage seen.

12 Ferric chloride used in 5 to 10 per cent sterile aqueous solution subcutaneously, produces marked necrosis, edema, and hemorrhage at the site of inoculation. Clinical jaundice does occur, and the extensive central

necrosis and hemorrhage in the liver must be listed as one of the causes of death. A single animal with a wet dressing of ferric chloride on its 60 per cent burn died on the eighth day and showed liver necrosis, with hemorrhage.

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ANIMAL EXPERIMENTS WITH TANNIC ACID
SUGGESTED BY THE TANNIC ACID TREATMENT OF BURNS
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SINCE ABOUT 1925,¹ tannic acid has been widely used in this country and abroad² in the treatment of cutaneous burns, by spraying on aqueous solutions, by bathing the patient in aqueous solutions, or by applying an ointment to the burned area. The concentrations of tannic acid in the preparations which have been employed have ranged from less than 5 to 20 per cent. The U S P tannic acid ointment has been made up with 20 per cent tannic acid, but in a tubed preparation recently acquired the tannic acid content is five per cent.

The local effects of the tannic acid have been advantageous in several respects. Pain has been relieved, a firm, dry coating or eschar has formed, and the nursing problem has thereby been rendered simpler. The dryness of the eschar, and probably some of the properties of the tannic acid, have inhibited bacterial growth. The disadvantages of tannic acid in the area of application have been pointed out.³ These include (1) Cracking of the stiff eschar, and curling of the edges, (2) too great stiffness of the eschar if the substance is applied to the face or perineum, and (3) masking by the eschar of underlying infection. In addition, tannic acid may destroy remnants of epidermis and hair follicles from which skin might regenerate in the stage of healing.⁴ The eschar may be difficult to remove.

The most serious drawback to the use of tannic acid to date is the suggestion that it is absorbed from the region of application and causes damage to the liver.^{5, 6} Since 1938, at least four communications^{2, 5, 7, 8} have appeared describing impressive central necrosis of the liver in patients who have been burned and have had some form of tannic acid therapy, whereas papers on fatal burns which appeared before the use of tannic acid do not emphasize hepatic necrosis as characteristic of burns.^{9, 10}

Evidence has begun to accumulate that tannic acid damages the livers of animals when it is absorbed from a burned area or from the subcutaneous tissues. Dogs burned experimentally and then treated with tannic acid ointment showed hepatic necrosis,⁸ but, since no control experiments were performed in which tannic acid was applied in the absence of the burn, the comparative role of burn and tannic acid in the production of hepatic necrosis is difficult to evaluate. Following subcutaneous injections of tannic acid (U S P) into white rats severe hepatic damage has been observed.⁵

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† One of us (P H) is indebted to the John and Mary Markle Foundation for its support.

These lesions consisted of central necrosis comparable to that noted in autopsies of burned patients who had been treated with tannic acid, and the degree of liver damage in the rats was in direct proportion to the amount of tannic acid injected subcutaneously. Some of the rats (70-90 Gm) which received a total dosage of from 0.15 to 0.4 Gm of tannic acid during a day or two, died within this period, while others were sacrificed on the third or fourth day, and usually showed hepatic necrosis. It was also stated that similar results were obtained after the injection of rabbits and guinea-pigs with tannic acid.

EXPERIMENTAL STUDIES

In the experiments to be reported it was desired to amplify those made on rats already mentioned,⁵ and to determine the importance of the various factors involved, in order to judge the applicability of tannic acid to the treatment of human burns, insofar as the experimental results might aid in the settling of this problem.

The following four series of experiments were undertaken, and will be considered subsequently under each heading.

(I) Experiments to verify the observation⁵ that subcutaneous injections of tannic acid produce hepatic necrosis.

(II) Experiments to determine whether tannic acid is absorbed when applied to a body surface denuded of skin.

(III) Experiments to determine whether tannic acid or some derivative thereof, can be excreted in the urine, after the subcutaneous injection of tannic acid.

(IV) Experiments to determine whether tannic acid (U S P) can be purified further, so as to avoid hepatic damage.

I—HEPATIC NECROSIS FROM SUBCUTANEOUS INJECTIONS OF TANNIC ACID

In rats, subcutaneous injections of solutions of tannic acid (U S P—Merck) produced hepatic necrosis, thus corroborating the experimental results in rats obtained by Wells, Humphrey, and Coll,⁵ previously mentioned. For example in a test with 11 rats (34-58 Gm each) tannic acid injected in divided doses subcutaneously, the total amount varying from 50 to 150 mg caused the death of four rats in 1 to 3 days. In those rats which survived and were sacrificed, microscopic study of the organs showed central necrosis of the liver, while microscopic study of the organs of five control rats injected subcutaneously with distilled water showed no necrosis of the liver. In addition, it was found that there was much necrosis at the point of injection of the tannic acid, and much inflammatory reaction, while no necrosis and minimal inflammation occurred at the point of injection of distilled water in the controls. (In no experiments were the solutions sterilized.)

Exactly the same type of experiments were carried out in 115 white mice (Table I), with the same results. It is seen that as little as 0.5 cc. of

0.5% aqueous solution (25 mg of tannic acid) produced hepatic necrosis and necrosis at the point of injection. The use of this concentration, similar to the use of greater strengths, resulted in the death of many mice. Of 30 control mice which received distilled water, only one showed any hepatic necrosis and none died. It seemed fair to conclude, therefore, that subcutaneous injections of tannic acid were often lethal for mice, and that hepatic damage was frequently produced. None of the other organs examined (heart, lungs, spleen, kidney) showed lesions.

TABLE I

EFFECT OF SUBCUTANEOUS INJECTIONS (0.5 CC PER INJECTION) OF TANNIC ACID (U.S.P.) ON WHITE MICE (12-30GM)

No. of Mice	Tannic Acid	No. of Injections	No. Died	Killed after	Total Dose	Local Necrosis	Lesion Inflammation	Liver Necrosis	Lesion Fatty Change
5	10%	1 or 2	4	2 days	50-100 mg	++++	+	++	0
8	5%	1 or 2	5	2 days	25-50 mg	+++	+	+	0
18	2.5%	1 or 2	11	2 days	12.5-25 mg	++	++	++	±
19	1%	1 or 2	9	2 days	5-10 mg	++	++	++	±
20	0.5%	1 or 2	10	2 days	2.5-5 mg	++	++	++	±
15	0.25-0.5%	4	0	4 days	6 mg	±	+++	0	+
CONTROL MICE RECEIVING DISTILLED WATER									
17		1 or 2	2	2		±	±	0	±
1		2	0	2		+	+	+	+
12		4	0	4		0	0	0	+

In Table I it is to be noted that the sublethal dosage was in the neighborhood of 0.5 cc of a 0.25% tannic acid solution. This amount could be given repeatedly without causing death or hepatic change visible microscopically. Of mice which survived after receiving larger doses and which were sacrificed after two days, the great majority showed central necrosis of the liver of varying degree (+ + indicates that necrosis was complete from the central vein outward for one-third of the radial distance to the periphery of the lobule). In some mice, allowed to survive much longer (not shown on Table I), hepatic lesions were not found, and it was thought that lesions had probably been present during the first several days and had then repaired by regeneration. However, carefully controlled experiments to prove this point were not successfully concluded. From general knowledge concerning the regenerative power of the liver, it seems probable that this is true.

Acidity of Tannic Acid Not the Necrotizing Factor—That the necrotizing effect of tannic acid at the area of application and in the liver was not due to the acidity of the drug, is shown by the results of injection of neutralized tannic acid as shown in Table III. Tannic acid (5%) brought to p_H 7.2 produced well-marked necrosis at the point of application and in the liver, nearly as marked as the original 5% tannic acid of p_H 3. In addition hydrochloric acid was adjusted to p_H 3 with sodium hydroxide, and when injected had no necrotizing effect on the liver, and only slight effect locally at the site of injection.

II—ACTION OF TANNIC ACID APPLIED TO A BODY SURFACE DENUDED OF SKIN

Unsuccessful attempts were made to duplicate exactly in the rat the therapeutic use of the drug on human burns. Burns were made by various

methods (flame, soldering iron, scalding, *etc*) but were unsatisfactory for experimental purposes for three reasons (1) The burn frequently affected the viscera through the thin wall of the rat, (2) the exact size of the burn could not be standardized, and (3) when the burn was large enough for test purposes the rats sometimes died from the direct effect of the burn.

Because of these drawbacks, no study has been made of the absorption of tannic acid from a burn, but data have been secured concerning the absorption of tannic acid from body surfaces denuded of skin. Such data are important because the burn is excluded as a complicating factor. But the inference should be carefully avoided that absorption from a burned area would be the same as from these experimentally produced wounds. Burns often have a layer of necrotic tissue which might produce conditions far different, with regard to the local and distant effects of tannic acid. Moreover, in certain burns the epidermis may not be destroyed, and there is evidence that the horny layer of epidermis may act protectively against tannic acid.⁴

If all of the skin of the thorax and abdomen were removed, in a zone encircling the trunk, the rats died of this procedure alone, too soon for any further experimentation. However by denuding the skin of the ventral surface of the abdomen and thorax, over an area of about 8 x 10 cm. in large rats, the rats survived satisfactorily. Such an area untreated remained moist for a time, and was usually somewhat moist after two days, when the control rats were sacrificed. The denuded areas had usually contracted somewhat by this time.

The procedure consisted of anesthetizing the rat with ether, denuding the ventral skin, and suspending the rat in the solution to be tested (tannic acid solution, distilled water, *etc*) for 15 minutes while the animal was still under the influence of ether. The amount of skin removed was always less than one-third of the whole body surface, usually about one-fifth or one-quarter. The following day the denuded area was washed with the test solution, without anesthesia of the rat, and at the end of the second day the rat was sacrificed with illuminating gas. When ointment was employed, it was thoroughly applied to the denuded area of the anesthetized rat and again on the following day, without anesthesia of the rat.

In experiments not included in Table III it was demonstrated that the shaved body surface or the severely scratched body surface did not permit the absorption of enough tannic acid to produce any hepatic necrosis. Also, it was shown that soaking the animal in tannic acid solution for 15 minutes produced no necrosis of the undamaged epidermis. This is probably due to the protective effect of the stratum corneum and the more superficial layers of the epidermis as emphasized by Taylor⁴ (who was able, however, to produce epidermal necrosis by repeated exposure to tannic acid over a period of several hours).

The experimental results following application to the denuded body

surfaces are shown in Table II. A few rats died apparently as the result of the treatment with the stronger aqueous solutions of tannic acid. (Two of the rats treated with 20% tannic acid, and the control rat treated with distilled water, were judged to have died because too much skin was removed.)

TABLE II

EFFECT OF TANNIC ACID APPLIED TO RATS PARTIALLY DENDED (LESS THAN ONE-THIRD OF BODY SURFACE) OF SKIN. RATS (136-398 gm) SACRIFICED ONE TO FOUR DAYS AFTER FIRST APPLICATION

Treatment	No. of Rats	Area		No. Killed after	Local Lesion			Liver Lesion		
		Denuded at Autopsy	sq cm		Necrosis	Inflammation	Bacterial Growth	Necrosis	Fatty Change	Mitosis
20% solution	16	35 sq cm		5	1-4 days	++++	+	±	+	0
20% ointment	6	35 sq cm			2 days	++++	+	++	+	±
15% solution	3	46 sq cm		1	2 days	++++	+	+++	+	++
10% solution	3	54 sq cm			2 days	++	+	+	±	0
5% solution	3	54 sq cm			2 days	+	+	±	±	±
5% ointment	3	53 sq cm			2 days	+	+	0	+	+
5% solution and 10% AgNO ₃	3	37 sq cm			2 days	++++	+	0	+	0
2.5% solution	3	51 sq cm			2 days	+	+	±	±	0
Distilled water	28	40 sq cm		1	2-4	±	+++	+++	+	0

Effect upon the Liver—Hepatic necrosis was usually, but not invariably, produced whether the aqueous solution or the ointment was used. There were individual variations among the rats. For example, the necrosis was of a high degree in one of the rats treated with 15% aqueous solution, the central three-fourths of each lobule being destroyed, while in the other two rats, which received this solution, the necrosis extended out about one-quarter of the distance from the central vein to the periphery of the lobule. None of the controls treated with distilled water showed any hepatic necrosis. In general, the hepatic damage produced was less severe than from small subcutaneous injections, a result which is perhaps not surprising, since the subcutaneous material might be absorbed into the lymphatics and blood vessels, and this absorption might go on for some time.

No hepatic necrosis was noted in the three rats treated with 5% tannic acid and 10% AgNO₃ applied alternately over a period of 30 minutes, with omission of all treatment on the following day.

There was no correlation between fatty change and the concentration of tannic acid. Mitoses were noted more often in the hepatic cells of livers which had been severely injured. No lesions were noted by microscopic examination in other organs (kidney, spleen, lungs, heart) which were examined routinely.

In a separate test on four rats, it was found that the application of a strong (20%) solution of tannic acid to small areas (6 sq cm) denuded of skin was attended with no hepatic necrosis.

Effect of Tannic Acid at Site of Application—Tannic acid often had a direct necrotizing action on living tissue when applied to a free subcutaneous or muscular surface. It was thought to coagulate the protein in the living cells at the site of application. A local effect of tannic acid on living cells has previously been claimed.⁴

Proof of the necrotizing action of tannic acid was obtained by comparing microscopic sections of the denuded abdominal wall of rats treated with tannic acid preparations with corresponding sections from rats treated with distilled water alone

When distilled water alone was used there was, of course, some superficial necrosis of the denuded surface due to the drying of the tissues, and other traumatizing factors and possibly early bacterial action. However in the great majority of rats treated with distilled water the necrosis did not extend through the fibrous sheath overlying the abdominal muscles to involve the muscle fibers. In the rats treated with tannic acid preparations, necrosis of this underlying muscle was usually noted, and sometimes it was severe. The necrosis of muscle resulting from immersion of the rat in 20% tannic acid, for example, extended, on the average, one-fourth of the way through the abdominal muscle mass in the denuded area. Necrosis from weaker preparations 2% and 5%, was at times no greater than that caused by distilled water, but in most cases was greater. In the three rats treated with 5% tannic acid and 10% silver nitrate the local effect on the muscle was about the same as that from the 20% tannic acid preparations but only three rats were treated with the combined drugs. Associated with the necrosis there was cellular inflammatory reaction and edema of the adjacent tissues. This was usually less prominent than in the rats subjected to distilled water. Bacterial growth was not demonstrated deep in the tissues in microscopic sections in any of the rats but in the rats treated with distilled water bacterial growth on the surface was regularly far greater than in the rats treated with tannic acid preparations.

III—METABOLITES IN URINE

A material which gave the ferric chloride test for tannic acid and gallic acid was demonstrated in the urine of rats which had received tannic acid subcutaneously. The exact nature of the substance could not be demonstrated, but the substance was not in the urine of normal controls injected subcutaneously with distilled water.

Rost,¹¹ in 1897, concluded from studies on cats and rabbits that tannic acid administered intravenously or subcutaneously does not pass unchanged into the urine but appears as gallic acid and, apparently also in the form of other, as yet unknown, products of tannic acid.

Tannic acid solution (1 cc of 5% solution) was injected with great care to prevent spilling, beneath the shaved skin of anesthetized (ether) rats. Urine was collected for 24 hours in a metabolism cage. As controls, distilled water was injected into anesthetized rats and the urine collected in the same fashion.

The urine from the rats which had received the tannic acid turned black or dark gray when ferric chloride (10%) was added, while the urine from the normal rats did not give this reaction. The possibility that a small quan-

tity of tannic acid had escaped from the injection site and had contaminated the collected urine was checked on by obtaining urine directly from the urinary bladder of one of the rats. The possibility that the material excreted was acetone bodies was excluded by means of a negative Rothera test for acetone, and the possibility that it was aceto-acetic acid was excluded by boiling the urine, thus destroying any aceto-acetic acid, and then obtaining the darkening of the urine on the addition of ferric chloride.

The darkening of the urine produced by ferric chloride in the rats injected with tannic acid matched the darkening produced in 0.1% aqueous solution of tannic acid, U. S. P. (0.1 in 0.1% normal urine solution of tannic acid, U. S. P.). Attempts to show that the material in urine from the rats which had received tannic acid was tannic acid by the precipitation of egg albumen were unsuccessful. *In vitro* experiments with tannic acid in normal urine, however, indicated that the urine, apparently, would inhibit the precipitation of egg albumen by tannic acid. Attempts to identify the material by absorption spectra were also unsuccessful, as were several other tests for tannic acid.

TABLE III

THE EFFECT OF GALLIC ACID AND OF THE ACIDITY OF THE EXPERIMENTAL SOLUTIONS UPON WHITE RATS (SUBCUTANEOUS INJECTIONS 1 CC. DAILY, TOTAL DOSE 100 MG. (ALL RATS SACRIFICED AFTER TWO DAYS))

No. of Rats	Local Lesion		Liver Lesion	
	Necrosis	Inflammation	Fatty Change	Mitosis
		5% gallic acid (pH 3)		
6	++	++	0	±
		5% neutral gallic acid (pH 7.2)		
6	+	++	0	±
		5% neutral tannic acid (pH 7.2)		
6	+++	++	++	±
		HCl acid (pH 3)		
5	+	++	0	±
		5% tannic acid (pH 3)		
5	+++	+++	+++	+++

Since gallic acid is a decomposition product of tannic acid, and since it has been stated to appear in the urine of cats and dogs given intravenous or subcutaneous tannin,¹¹ tests were made with this crystalline substance, to see how closely it resembled tannic acid in its effects on rats. Rats injected with gallic acid produced urine which gave an intense ferric chloride reaction.

However, evidence was obtained that gallic acid was not the portion of tannic acid responsible for hepatic necrosis (Table III), for when 5% gallic acid was injected subcutaneously (100 mg.) no hepatic necrosis was obtained.

In brief, it was demonstrated that the urine of rats which had received tannic acid subcutaneously blackened when ferric chloride was added. Thus, while the phenolic substance in these urines has not been positively identified, there is presumptive evidence for the circulation of tannic acid or its derivatives in these rats. In any analysis of the mechanism of the production of hepatic necrosis this factor must be considered. Moreover, the necrotizing effect of tannic acid on the liver was probably not due to the gallic acid component of tannic acid.

IV—ATTEMPTS TO PURIFY TANNIC ACID

It was desired to determine whether or not the effects of tannic acid (U S P) on rats and mice were due to the tannic acid itself or to extraneous substances present in this material. Accordingly, several attempts to obtain crystalline tannic acid were made in the following manner. To 25 cc of two-thirds saturated tannic acid were added 15 volumes of saturated sodium chloride solution. The tannic acid was kept in a bath maintained, in consecutive experiments, at -10° , 0° , 10° , 25° , 37° C. The sodium chloride was added drop-wise over the course of eight hours in all but two instances. The experiments at 0° and 25° C were continued for 24 hours. The sample of tannic acid which precipitated in each trial was used again in the next trial. In no case was a crystalline product obtained, although the samples were contaminated with considerable quantities of sodium chloride.

The last sample so obtained was extracted with 50 cc of hot, absolute alcohol to free it of sodium chloride, which was filtered off. The alcoholic extract was then evaporated to dryness *in vacuo* and the residue taken up in water. An excess of barium hydroxide was added at 50° C, and the precipitate was collected by centrifugation. The precipitate was washed with three portions of hot water and then resuspended in dilute sulfuric acid and the barium sulfate precipitate was discarded after the solution no longer gave a precipitate with sulfuric acid. The tannic acid was again precipitated with sodium chloride, dissolved in an equal mixture of hot alcohol and acetone and precipitated with ether. This precipitate was again suspended in water and the tannic acid was precipitated with sodium chloride. No determination of the salt content of the dry precipitate was made.

This cleaned product had the properties of tannic acid. It turned black with ferric chloride solution and precipitated egg albumen. It tanned the rats' abdominal wall which had been denuded of skin and caused necrosis of the superficial portion of the abdominal musculature just as strong tannic acid solution would do.

In 21 mice, subcutaneous injections of the cleaned material was followed regularly by hepatic necrosis when solutions of 1% or greater were given.

From these results it was concluded that the cleaned tannic acid had the same action in the experimental animal as the tannic acid (U S P), and, furthermore, that the procedures used had in no way lessened the untoward action of tannic acid on the liver. Therefore the necrotizing action of commercial tannic acid (U S P) would seem to be due to tannic acid *per se*, and not to any contaminating material.

APPLICATION OF EXPERIMENTAL RESULTS TO THE TREATMENT OF HUMAN BURNS

The Local Necrotizing Effect—The experiments in rats suggest that if tannic acid came in direct contact with undamaged human subcutaneous tissues or muscles some necrosis would result, and that if the stronger preparations of tannic acid 20%, came into contact with undamaged muscle there would be necrosis to a depth of five to ten muscle fibers. Applied to the human

abdominal wall denuded of skin, the necrosis would not extend one-quarter of the distance through the muscle mass or a distance anywhere approaching this fraction as it did in the rat because of the much greater thickness of the human abdominal muscle mass

But it should be constantly borne in mind that the human third-degree burn is not simply an area denuded of skin, but is an area on the surface of which there is usually necrotic tissue caused by the burn. It may be that this necrotic tissue would prevent the underlying viable tissue from suffering the necrotizing action noted in the rat. The degree of ease with which tannic acid penetrates necrotic tissue is not known.

The local damaging effect of tannic acid would be of little consequence in deep burns because the loss of a few additional strands of tissue would not matter. The damaging effect might be of greater importance when remnants of hair follicles and epidermis were destroyed and might interfere with the regeneration of epithelium.⁴ In a recent human burn of second-degree treated with tannic acid in 5% concentration, however, regeneration of epithelium was sufficiently rapid to indicate that the local necrotizing effect if present at all, had no significance. (Personal observation, R. D. B.)

In brief, it might be argued that the only precautions to be observed, so far as the local lesions are concerned, is not to use high concentrations of tannic acid (15 or 20%), and to bear in mind the possible necrotizing action of the drug in those burns which are partially of second and partially of third-degree.

The Effect on the Liver —The experimental data can not be applied directly to the human case of burns because it is not clear that the absorptive power of a burn is the same as that of a body surface denuded of skin. The evidence that tannic acid can be absorbed through a burned area rests on the observations made at autopsy upon human cases of burns and on experiments on dogs.⁶

These experiments on rats suggest that in human burns absorption of tannic acid might be expected from the ointment and from baths of the aqueous solutions to about the same extent and that minor degrees of hepatic necrosis would be of brief duration, not permanently damaging, and of no consequence, while severe degrees of necrosis might be associated with a fatal outcome.

SUMMARY AND CONCLUSIONS

1 Experiments with rats and mice have corroborated experiments by others that death and hepatic necrosis can be produced by the subcutaneous injection of tannic acid.

2 Neutralized tannic acid of pH 7.2 injected subcutaneously was as damaging to the liver as the tannic acid (U. S. P.) of pH 3.

3 Gallic acid introduced subcutaneously produced no hepatic damage, indicating that it is not the gallic acid component of tannic acid which is responsible for the necrosis of the liver.

4 Hepatic necrosis was produced in rats by removing the ventral skin, immersing the rat in a tannic acid bath (15 minutes) and washing the treated area with tannic acid the following day. Minor hepatic necrosis occurred in some of the rats when one-fourth of the skin of the body was removed and solutions as low as 2.5% were applied. Severe hepatic necrosis was produced by 20% tannic acid applied to an area of the same size, and some of the rats which received this concentration died. In control experiments in which other rats were treated with water in the same manner, no hepatic damage was noted.

5 Tannic acid produced hepatic necrosis whether aqueous solutions or ointments were used.

6 Tannic acid of 10%, or less, sometimes produced necrosis of viable tissue over the denuded areas, and regularly when concentrations greater than 10% were employed.

7 A substance which turned black on the addition of ferric chloride was demonstrated in the urine of rats which had received tannic acid subcutaneously.

8 Direct application of these experimental results to the treatment of human burns with tannic acid should be made with extreme caution, especially those dealing with absorption from a skinned area, since absorption from burns has not been investigated in this study.

The authors wish to acknowledge the assistance of Mrs. Margery Prindle, M.A., in this study.

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A CLINICAL TEST FOR DIFFERENTIATING SECOND FROM THIRD DEGREE BURNS*

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IN THE PAST, decision as to whether a burn was second or third degree at the outset, has rested on gross inspection, its value being dependent on an individual's experience with large numbers of burns. There have been many instances, however, in which it was impossible to tell the true extent of the injury until considerable time had elapsed after the reception of the burn, and decision as to the ultimate treatment has had to be postponed.

The idea is receiving increasing acceptance that an excellent treatment for third degree burns, if not too extensive, is immediate excision of destroyed tissue, followed by grafting. Before undertaking this, however, one must accurately delimit those areas in which skin regeneration is possible, from those in which the entire cutis is destroyed both in order to take advantage of any remaining cells as foci of growth, and to eliminate as rapidly as possible the dead tissue so that granulations with subsequent scar tissue formation may be minimized.

It is the purpose of this communication to present a clinical method of distinguishing between burns of second and third degree, which is applicable shortly following injury.

METHOD—Lange and Boyd,¹ and Herrlin, *et al*,² have shown that sodium fluorescein injected intravenously may be employed to reveal "the presence and adequacy of the circulation," and have suggested its use in measuring the circulation time, determining the viability of the bowel in experimental and clinical cases of strangulated hernia, and in cases of gangrene of the extremity, where it is desired to demarcate satisfactory circulatory levels for amputation.

With this in mind, experimental animals (rabbits and dogs) were burned by means of a steam-heated hot plate applied to the shaved skin. Third degree burns were produced, as proved either by excision and examination of the involved area, or by subsequent sloughing and granulation. Immediately after burning, five to ten cubic centimeters of sodium fluorescein was administered, and the area viewed under ultraviolet light screened with a Wood filter. The burned areas appeared as sharply demarcated blue-black patches in contrast to the surrounding yellow-green color of normal fluorescein-containing skin. The next step was an attempt to produce milder burns. Since it is fairly well established that second degree burns comparable to those encountered in man may not be produced in the usual laboratory

* This study was carried out under a grant from the Wallace and Tiernan Products, Inc.

animal,^{*} human volunteers[†] were given second degree burns which blistered, desquamated, and subsequently healed without granulation. Following each burn ten cubic centimeters of 20% sodium fluorescein was given intravenously, and the burned sites examined as above. In every instance the areas appeared yellow-green generally more intense in color than the surrounding skin.

Finally, a similar test was performed in six patients who had suffered accidental burns. At the time of application of the test, it was desired to know whether both second and third degree burns were present, and, if so, to separate them. As in the experimental burns, third degree areas were black, while second degree burns were yellow-green in color, the two being readily distinguishable from one another. The accuracy of the delimitation by this method was subsequently proved after sufficient time had elapsed, by the natural demarcation. Kodachrome pictures were taken and the color contrast presented was readily apparent.

COMMENT —In evaluating this test, the basic pathologic differences between second and third degree burns should be borne in mind, as well as their rôle in the production of the color contrasts. For simplicity we consider a second degree burn to be one in which not all of the skin epithelium is destroyed, thus permitting regeneration if only from the cells of the hair follicles and sebaceous glands. A third degree burn embodies complete destruction of the epithelium, and postulates granulation. Fluorescein when administered intravenously diffuses throughout the vascular tree and after a sufficient time, some of the drug undoubtedly enters the intercellular fluid and stains the cells. In normal skin, it permeates into all the minute vessels of the corium, even the subepithelial capillaries, and may be visualized on the surface. On the other hand, if enough tissue destruction has occurred, as in a third degree burn, vascular transportation of the drug to the upper and visible skin layers is impossible. However in any one area, some vessels may be intact, while others are destroyed, and it is here that a mottling of color occurs suggestive of a deep second degree burn as opposed to the diffuse yellow of a more superficial injury. With some practice one may easily appreciate this difference.

We have given no more than ten cubic centimeters of sodium fluorescein to any one patient, although more has been used in another clinic.¹ We have found that there is clinical evidence of its presence in the blood stream by visual skin discoloration for about 10-12 hours following administration and that its presence in the urine is noted for about 30-40 hours. In our experience, it appears to be a safe drug for intravenous use in such dosage the only untoward symptoms being a transient nausea if given too fast (three patients), and a questionable attack of renal colic in one hypochondriacal individual, which occurred two days following its administration and was unaccompanied by objective urinary findings. We have noted no ill effects

* Save, in our experience, a suckling pig.

† Students of Cornell University Medical College.

from the accidental subcutaneous extravasation of the drug in animals or humans

SUMMARY

A method of distinguishing second from third degree burns is introduced which has proven reasonably accurate in a small series of cases and depends only on the recognition of sharply opposed color contrasts. It is hoped that its widespread application may aid in preventing some of the unfortunate end results of accidental burns, and may cut down appreciably the duration of hospitalization of such patients making the initial prognosis more accurate.

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PILONIDAL SINUS

APPLICATION OF PLASTIC SURGICAL PRINCIPLES IN A NEW SURGICAL APPROACH

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THE IMPORTANCE TO THE ARMY of the treatment of pilonidal cysts is very real, as may be inferred from the mass of literature being presented relative to them recently. The condition is usually considered a minor one, but the morbidity incident to a conventional radical excision, which obviates the likelihood of recurrence, is a major problem.

The embryology of pilonidal sinus has been studied by many investigators. Two tenable theories of origin have been evolved. The one bearing the bulk of substantiating evidence is that the sinus is derived from epithelial cells of the neural tube which fail to dissociate during prenatal life when other elements of the embryonal "tail" do so. The other theory is that the sinus is derived from an invagination of epidermal elements during embryonic life. Contention over these theories has entertained embryologists, but a settlement of the argument would not provide the clinical surgeon with a solution of his problems.

However, we do learn a great deal from the study of the pathology of the condition. First of all, and most important in the establishment of an operative approach, is the fact that the sinus is a disease of the subcutaneous fat and not a disease of the skin. There are usually, but not always, dimples of small size in the sacrococcygeal region, which form the only connection with the skin, except where artificial ones are made by surgical incision or spontaneous rupture of an abscess. These dimples and artificial openings have no surgical significance *per se*, but are important only if they connect with the epithelial-lined tract in the subcutaneous fat. This pathologic fact is emphasized because it is overlooked in most discussions of the subject and because it makes it obvious that the removal of skin is unnecessary if the subcutaneous fat can be adequately exposed and resected without it. Second, it is impossible to determine the extent of the epithelial tract in a given case by any clinical test, be it injections of dyes, radiopaque substances, or the passage of a probe, because the tract may be occluded with pus and débris, or the lumen so small that it will not admit any of these materials. This fact makes it necessary to remove an adequate amount of fat surrounding the tract or recurrences will appear. Third, infection is almost invariably present in the tract which is causing symptoms. Primary closure fails so often because infection leads to fat necrosis which, in turn, leads to wound separation and the formation of dead space. This dead space is in reality, another sinus, and must be treated by incision and packing. Provision for adequate drainage is a strong point on the side of radical excision with open

packing, but prolonged healing time makes this procedure undesirable. Fourth, is an anatomic feature of the region. The gluteal muscles exert a pull on the skin and subcutaneous fat which is a prime factor in the formation of dead space under an incision which has been subjected to primary closure. It will also cause a poor result in the so-called "partial primary" closures because the sutures maintaining the closure will cut through and allow the wound to gape. Restraint with adhesive, or other devices, is of no avail in preventing the dogged-tug of these muscles. A sound surgical approach should include a release from this lateral pull on the wound.

The number of methods suggested in the literature for the relief of this condition is legend, and would not bear enumeration, but the basic principles underlying approaches are not at great variance and should be a part of the armamentarium of anyone entrusted with the care of these patients. The basic features of suggested surgical approaches are as follows: (1) Radical excision, with open packing. (2) Radical excision, with immediate primary closure. (3) Radical excision, with closure by flaps detached from the adjacent area. (4) Radical excision, with partial primary closure. (5) Radical excision, with delayed partial primary closure. (6) Destruction of tract with sclerosing solutions or cauterization. (7) Exteriorization of tract by incision and open packing with gauze. (8) Excision of tract with cautery or sharp dissection by undermining of wound edges, followed by partial primary closure.

Reference to the preceding paragraphs will suggest the advantages and disadvantages of these methods. We may emphasize that any method which falls short of radical excision is fraught with the likelihood of recurrence, and that primary closure after radical excision, with sacrifice of skin, is known to be treacherous because of the probability of wound separation.

All methods of radical excision so far suggested entail the sacrifice of skin primarily because it has been deemed impossible to provide adequate exposure of the underlying tract in the fat without this sacrifice. The method which we shall describe provides for this exposure by the undermining of four flaps, and a tract of any size can thus be exposed. It may be noted that this method is particularly applicable to the extensive tract in which sacrifice of a large amount of skin is customarily practiced. In the series reported, there have been a total of 49 cases. Ten cases had very small and superficial tracts which were treated by a method involving some type of partial primary closure and a method which we developed in the process of evolution of the more perfected procedure. Thirty-nine cases were treated by the method to be described. These facts suggest only that the large majority of cases fall into the extensive group and must be handled by radical methods.

In the 39 cases subjected to this method of treatment the average healing time was 38 days. The shortest healing time was 23 days, and the longest 61 days. Two cases returned about one month after discharge from the

hospital complaining of a draining site over the sacrum. In both cases one of the cotton mattress sutures had become imbedded under the skin. After removal of these sutures the wounds healed readily. This experience has led us to cut these sutures longer at the operating table so that they may be more readily identified at the scheduled time for their removal. Apology must be made for the fact that a long-term follow-up is not available in this series. However we feel free to believe that the recurrence rate will not be any greater than that already established for other procedures entailing the radical removal of fat from the sacrococcygeal region. The first of these operations of the reported series was performed September 9, 1942.

TECHNIC OF OPERATIVE PROCEDURES

Adequate exposure of the fat containing the tract is provided by three incisions. Two sides of a triangle on each side of the natal cleft are made with the apex of these incisions about one inch from the midline. Each limb is made approximately one and one-half inches long. The apices of these partial triangles are joined across the midline by another incision. The incision is carried only through the skin. For subsequent use for traction on the flaps, sutures are placed on the edges of these incisions at strategic points. The lower flap is then undermined by sharp dissection to a point well below the coccyx. The flap is not stripped entirely of fat, but the under surface of the skin is so exposed that a tract running close to it could be easily discovered. The upper flap is undermined in the same manner to a point well above the upper border of the sacrum. One tract is illustrated which extended very high in this direction. More exposure of the underlying fat can always be provided by extending the limbs of the incomplete triangles on both sides either up or down, as the case may require. The lateral flaps are formed by the undermining of the incomplete triangles down to their bases. It will be noted that these flaps are designed so that they have very broad bases which make sloughing of the tips unlikely. We have encountered very minor sloughing in only two cases. The extent of these sloughs was no larger than some of the stab wounds which we have purposely made and did not delay healing time.

Up to this point the tract in the fat has not been attacked but it is now thoroughly exposed by retraction of the flaps and may be removed *en bloc*. No hard and fast rule can be set forth as to the amount of fat which should be removed but it should be generous. Lack of exposure has been eliminated, and we have found that the small amount of fat left on the flaps will proliferate and provide a soft, pliable pad over the sacrum and coccyx in a very short time. Patients have not complained of pain and tenderness in this area upon return to their duties. The removal of the "block" containing the tract should be systematic and should lay bare the medial aspects of the glutei as well as the fascia over the lower lumbar region, sacrum and coccyx. Rigid hemostasis is secured in the base of the wound and on the flaps. The wound is then thoroughly

FIG 1



FIG 2



FIG 3



FIG 4

FIG 1—Primary Incisions. Probe is inserted into portion of tract, tract also extended downward toward coccyx but would not admit probe. This is true of a great many tracts and serves to emphasize the inadequacy of the probe in determining the limit of excision.

FIG 2—Flaps have been dissected free. Tract is exposed and ready for removal. Probe still lies over part of tract which will admit it.

FIG 3—The fat is being removed *en bloc* with the aid of traction. The surface of the sacrum and medial aspects of the glutei are exposed.

FIG 4—A block of fat over the sacrum and coccyx have been removed. A very small amount of fat has been left on the flaps.

bathed with warm normal saline solution in large amounts. By retracting upward on the flaps a large cup can be made of the wound and the solution poured in. Any bleeding produced by this bathing should be rigidly controlled. Any tabs of fat which float and are loosely attached should be debrided. This cleansing and debridement and attention to hemostasis all contribute to the production of a clean postoperative wound. Five Gm of sulfanilamide powder are then sprinkled into the wound with a salt shaker. Stab wounds are made in all flaps according to the pattern shown in the illustrations. These provide drainage for a potentially, or actually, infected wound. They would also serve to make the flaps longer if this were necessary, but it will be found that the flaps fall into their original positions without the slightest tension in any direction. In fact, one frequently finds more tissue than he needs and is able to debride the dimple site. This may be done in every case if desired. Points where spontaneous rupture of an abscess has occurred remote from the dimple site, may be removed by making a stab wound involving this area. The central flaps which cover the sacrum and coccyx are free of lateral pull by the glutei, and dead space will not be created by lifting of the flaps. The flaps are secured in position by mattress sutures placed at strategic points. These sutures are passed through the skin, then engage the underlying bed of the wound securely, then pass back through the skin and are tied. No sutures are placed in the edges of the wounds to provide apposition of the incisions. The incisions fall together naturally when the flaps are replaced. Close apposition is not desirable because of the potential danger of infection. When the mattress sutures are placed a row of them is left long on each side about three-quarters of an inch from the midline. These are tied across a gauze roll, about two inches in diameter and about four inches long, which lies in the natal cleft and maintains pressure on the central portions of the flaps. This gauze roll is impregnated with glycerin, which preserves the soft consistency of the pack and prevents it from becoming malodorous as it accumulates secretion from the wound. A pressure dressing of cotton waste is then applied. This top dressing is changed as necessary, but the gauze roll is left in place for approximately one week. Since it is held in place with sutures no amount of movement, straining at stool, or other activity can dislodge it. The mattress sutures are left in place from 10-12 days. Patients are allowed food as soon as it is tolerated, and no attempt is made to restrain bowel movements. Sitz baths are begun after the tenth day and continued until healing is complete. The patients are able to go to the bathroom as soon as they have recovered from the spinal anesthesia, and are allowed freedom of movement after the third postoperative day. An adjunct to treatment is the administration of the sulfonamides by mouth before and after operation as well as applying it directly to the wound. We have not used this adjunct universally. Gross infection has appeared in a large percentage of our wounds, but the presence of multiple stabs in the flaps has provided adequate drainage, and floating of the flaps has not

FIG 5



FIG 6



FIG 7

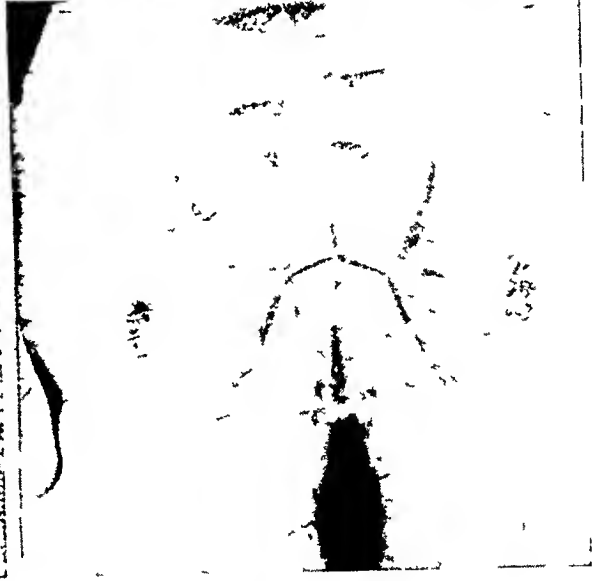


FIG 8

FIG 5—Stab wounds have been created in the flaps. The wound has been thoroughly cleansed by irrigation with saline. The floating fat is debrided. Bleeding caused by the irrigation is rigidly controlled. Sulfanilamide is sprinkled in the wound. Mattress sutures are placed at strategic points on the flaps. The probe is pointing toward the suture as it engages the fascia over the sacrum deeply. The sutures on the inferior flap have been drawn taut to demonstrate the replacement accomplished.

FIG 6—Replacement of flaps has been accomplished. Sutures have been left long in a row alongside the natal cleft. These will be used to hold the dressing in place. The original incisions fall together naturally, but sutures are placed in them to prevent overlapping.

FIG 7—A gauze roll impregnated with glycerin has been placed in the natal cleft and secured with the sutures which were left long. A further pad of cotton waste is placed over this dressing and held in place with adhesive tape. The latter can be changed whenever it becomes soiled. The former is left in place from seven to eight days.

FIG 8—The Healed Wound. The skin becomes resilient and freely movable over the sacrum and coccyx.

occurred. Infection has not deterred healing as far as we have been able to determine. We expect infection and provide for it.

During the evolution of this technic two other flap type operations were tried and found to be inadequate. The first was a T-shaped incision with the short limb of the T about one and one-half inches from and



Fig. 9.—The tract has been laid open and outlined with cotton thread. A generous amount of fat has been removed around it.

parallel to, the midline. The long limb of the T extended across the midline near the midsacral region. The undermining of flaps was found to provide inadequate exposure for the extensive case, and the tendency for flaps to "rise" was great because of inadequate release of lateral tug by the glutei. The second was the making of another lateral incision at the base of the long oblique limb of the T. This provided two lateral incisions which were staggered, that is, at different levels on the two sides of the transverse wound. Undermining provided adequate exposure but a tendency to floating of the flaps was again encountered. Adequate disposition had not been made of the tugging glutei.

One incident should be mentioned in order to avoid a repetition of it. A long coccyx whose tip was curved posteriorly was encountered in one case. This protruding tip was not removed. At the first dressing it was found presenting itself through a stab wound. It was necessary to remove this protruding tip at a later date. It would have been much better to have removed it at the operating table although healing was not impaired because of failure to do so.

We believe that the procedure, as it was finally evolved, attacks the basic problems presented by the pathology of this troublesome condition. Adequate exposure is provided so that the tract can be removed in a radical manner. Unnecessary sacrifice of skin is eliminated without jeopardizing the extent of excision. The unfavorable effects of infection are eliminated by the provision for adequate drainage through stab wounds. The lateral tug of the glutei on the flaps is eliminated by the incisions made on each side during the formation of the flaps.

CONCLUSIONS

(1) Radical and extensive removal of the subcutaneous fat of the sacro-coccygeal region is essential to the cure of pilonidal sinus without the likelihood of recurrence.

(2) A procedure making use of basic plastic and general surgical principles is presented which eliminates the sacrifice of skin and still provides adequate exposure of the fat which should be excised.

(3) Healing time has been consistently short for a radical excision of the cyst.

(4) Hope is expressed that others will see fit to try this procedure while the present mobilization of young men in the army provides such a rich opportunity for the continuous and consecutive observation of a large group of cases.

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SYNOVIAL CYSTS OF THE POPLITEAL SPACE CLINICAL SIGNIFICANCE AND TREATMENT

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THE PURPOSE of this paper is (1) to record further clinical experience with synovial cysts of the popliteal space, (2) to emphasize that these cysts often cause symptoms which suggest internal derangement of the knee joint and that unless the popliteal space is carefully examined the presence of such a cyst may well be missed, and (3) to point out that excision of the cyst relieves symptoms and results in excellent function of the knee joint

In a previous paper¹ the literature on this subject was reviewed, as well as the origin of the eponym, "Baker's cyst" frequently employed to describe synovial cysts of the popliteal space

ETIOLOGY

Synovial cysts of the popliteal space are due to a posterior herniation of the knee joint capsule or to hyperplasia—"fluid distention"—of one of the adjacent bursae, most frequently the semimembranosus bursa. In my experience, herniation of the joint capsule has been the most frequent cause for the condition. Wilson, Eyre-Brook and Francis² consistently found that the cyst was on the medial side of the popliteal space, originating from, or a part of, the semimembranosus bursa. Therefore, they concluded that the synovial sac is a congenital deviation of the normal structure.

Of those patients shown at operation to have true posterior herniation of the knee joint capsule, the majority give a definite history of trauma, particularly of a sudden, forcible hyperextension of the knee joint. The propensity of patients to ascribe a condition to some injury is well known. But the type of trauma described, that of hyperextension of the knee, is not so frequently encountered. In this group of cases, such an injury seemed to be of real significance as a causative factor in the development of the herniation.

On the other hand, of those patients known to have an hyperplastic bursa as the cause of the synovial cyst, a history of trauma was obtained in 75 per cent. However, in no single instance was it a type of injury that resulted in forceful hyperextension of the knee.

Upon operation, four children, in the age group of 5 to 12 years, exhibited enlarged semimembranosus bursae, which bears out the point made by Wilson, *et al*,² namely, that one would not expect a hernial protrusion in a joint capsule in a child. One of these cysts was recurrent, the child having been operated upon twice elsewhere. In this patient, who gave a definite history of recurrent swelling of the knee, a large communication with the knee joint capsule was demonstrated.

PATHOLOGY

The histologic examination of the lining membrane of the synovial sac, whether it was a hernial protrusion or an enlarged bursa, revealed a true mesothelium similar to the synovial membrane of the knee joint. Acute and chronic inflammation of the serosa was evident, together with moderate to marked round cell infiltration of the subserous layers. In the case of posterior herniation, the outer wall of the sac, especially that immediately

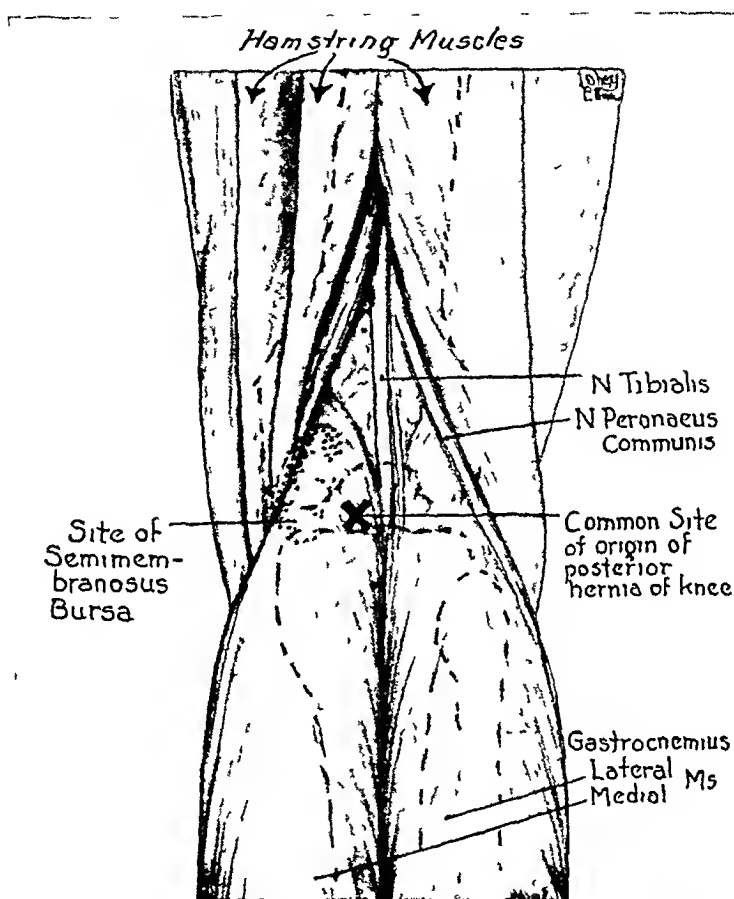


FIG 1—Both the semimembranosus bursa and the usual site of origin of posterior herniation of the knee joint are located beneath the medial head of the gastrocnemius muscle. A large synovial cyst from either source will fill the popliteal space and, as described, extend down the lower leg.

adjacent to the site of origin, was composed of relatively dense, fibrous tissue similar to the capsule of the knee joint, while the more distal portion of the sac was composed of fine connective tissue, quite friable and easily torn. This distal part of the sac was always firmly adherent to the adjacent fibers of the gastrocnemius muscle, especially the medial head. In patients shown to have a true posterior herniation there was a communication between the cyst and the knee joint. Of this group, 60 per cent gave a definite history of intermittent swelling of the knee, and presented a picture strongly suggestive of internal derangement of the articulation. Of those patients found to have a distended bursa as a cause of the synovial cyst, 20 per cent reported intermittent swelling of the knee, and in each instance in this group a communication with the knee joint was established at operation.

CLINICAL FINDINGS—INCLUDING ROENTGENOLOGIC EXAMINATION

Patients with synovial cysts of the popliteal space most frequently request medical advice because of aching discomfort in the knee, often associated with recurrent swelling of the joint. All the patients with relatively large cysts also had noted intermittent swelling of the lower leg and ankle region, particularly evident after standing for a long period of time. The longest duration of symptoms was six years, and this particular patient reported intermittent swelling in the popliteal space and at times in the knee joint itself for an interval of four years before operation. From four patients who had noted the swelling in the popliteal space, as well as intermittent effusion in the joint, a detailed history revealed that appearance of fluid in the knee coincided with sudden diminution in swelling in the popliteal space. The general character of the symptoms was indicative of an internal derangement of the knee joint.

On clinical examination these synovial cysts present themselves as a cystic swelling, the major part of which is distal to the transverse flexion crease of the popliteal space. The swelling has a definite elastic sensation of contained fluid, and in a typical case, with the knee flexed, a ball-like cystic mass in the popliteal fossa can be demonstrated.

Except in obese patients, these cysts are visible on inspecting the popliteal space when the extremity is placed in the position of hyperextension of the knee joint. Swelling due to an enlarged semimembranosus bursa is more obvious on the medial side of the popliteal space, while that due to a posterior herniation is found at or near the mid line (Fig 1).

The usual routine examination of the knee rarely exhibits any tenderness along the joint line and, as noted, there may or may not be increased fluid within the knee joint. Instability of the joint was not encountered.

In this group of cases the roentgenograms of the knee region consistently were negative, except in older patients in whom there was some degree of degenerative arthritis.

No attempt was made to inject air or oxygen into the cysts. Past experience with arthrograms revealed that this procedure created an appreciable irritation of the synovial tissue, and since surgery offers the one measure for cure of these cysts, such studies did not seem indicated. No attempt was made to aspirate the cysts, because in the majority of cases the thick contents would have necessitated the use of a large needle. Furthermore, as the cysts are multilocular, one would not expect to secure all the contents by aspiration.

OPERATIVE TECHNIC

After the first two cases, the remainder of the patients in this group were operated upon through a midline incision over the popliteal space (Fig 2), because it was not possible to foretell accurately the extent to which the synovial cyst had extended down the leg. In six patients, for example, the distal tip of the sac was well below the midcalf region.

Therefore an incision in the midline made the dissection much easier and more direct. With one exception there was no keloid formation in the scars. In that instance an infection of the superficial layers of the wound developed as the result of a thrombophlebitis which began in the lower leg and progressively advanced up the extremity until it reached the popliteal region, when the superficial portion of the wound became infected and had to be packed open. A tourniquet is not employed as bleeding is comparatively minimal.

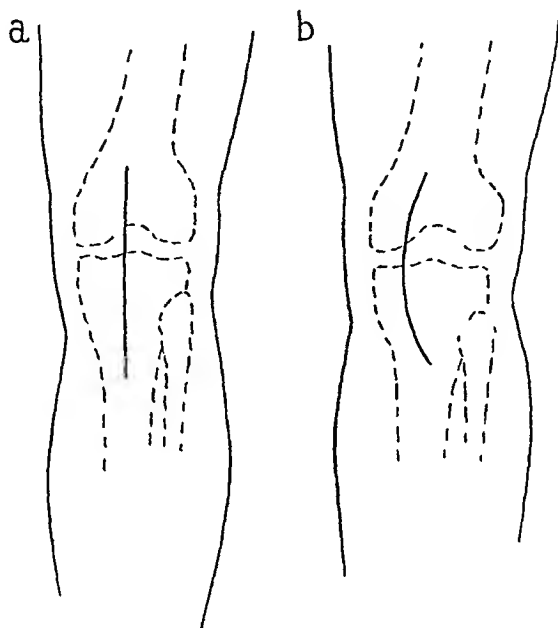


FIG 2—Diagram of types of incision. (a) As the operation is now carried out. (b) As performed in the early cases.

The deep fascia is incised in line with the skin, and with blunt dissection in the popliteal space, the underlying cyst comes into view. Then the incision is lengthened according to the extent of the cyst. The cyst wall is firmly adherent to the underlying tendon of the gastrocnemius muscle. Dissection begins in the distal part of the incision, and freeing of this cyst necessitates cutting away some of the tendon fibers, thus gradually progressing toward the midpopliteal region.

In a posterior herniation, the sac often exhibits a short, thick neck as the communicating channel between the cyst cavity and the knee joint. This is carefully defined, clamped, cut, and if sufficient tissue is present the stump is inverted, and the aperture then closed with interrupted silk sutures.

When a communication with the knee joint is demonstrated, every effort should be made to close this opening. In some instances, particularly with hyperplastic bursae, this is difficult as the opening into the joint may vary from one to three centimeters in diameter, with relatively rigid walls. In such a case, fibers from the adjacent tendon are cut for suture material or fascia lata is employed to close the defect. I believe that the care exercised in closing this aperture into the knee joint accounts for the fact that

no definite recurrence has been observed. In one patient the cyst may have recurred, but he has insufficient symptoms to submit to reoperation.

The concluding step in the operation, just before the cyst is actually removed, is to open it widely and carefully examine the inner wall, to determine, if not already known, the point of origin and whether the cyst communicates with the knee joint. The inner surface of the cyst presents numerous ridges and multilocular compartments, all of which should be

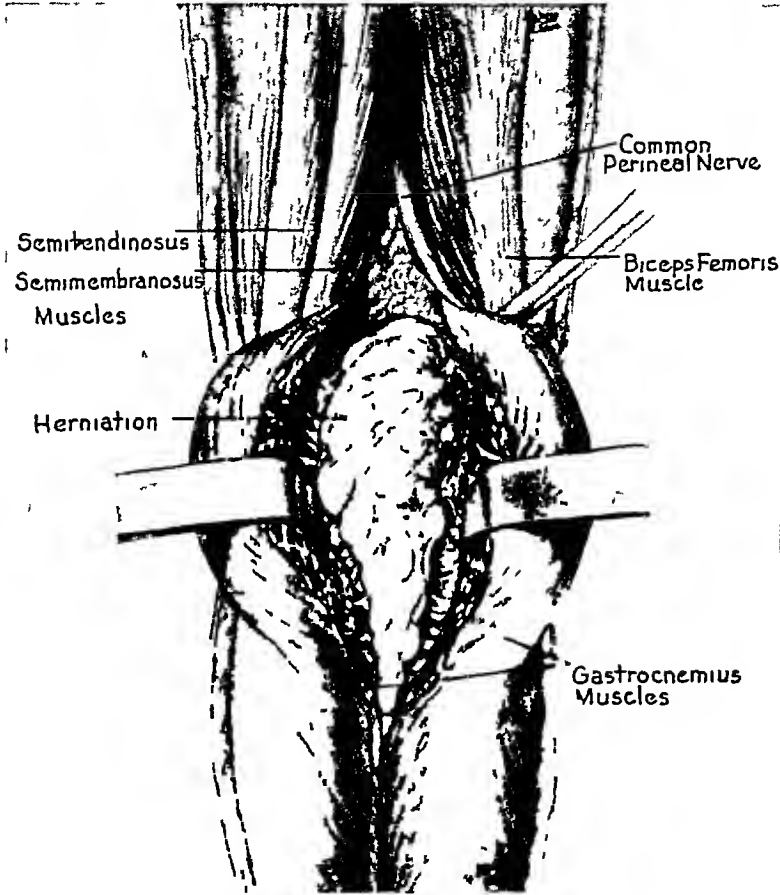


FIG. 3—Synovial cysts of the popliteal space due to posterior herniation of the knee joint. To obtain this degree of exposure it is necessary to cut away many of the tendon fibers from the gastrocnemius muscle. The cystic, friable distal portion of the cyst is well shown. The part outlined and not yet exposed is, as a rule, a fibrous band, always firmly attached to the gastrocnemius muscle.

investigated, because in three cases of enlarged semimembranosus bursa there were two separate openings into the knee joint. Hemostasis having been completed, it is important to resuture the deep fascia accurately.

Following closure of the wound, the patient is moved from the prone position, in which he was operated upon to the supine position, and a plaster encasement applied from the high thigh to the ankle, with the knee in full extension. This encasement is left on for ten days, the objective being to obtain early healing of the wound with the joint in full extension. Furthermore, this position aids in preventing undue oozing. Thirty-six hours

after operation the patient is strongly urged to start active contraction of the quadriceps muscle, which he continues during the convalescent period

In every patient in whom a definite communication between the synovial cyst and the knee joint was demonstrated, there was an appreciable post-operative effusion into the knee joint. In consequence, the convalescence and return to normal function in the early cases operated upon was delayed because of inability to overcome flexion of the knee. With the use of the

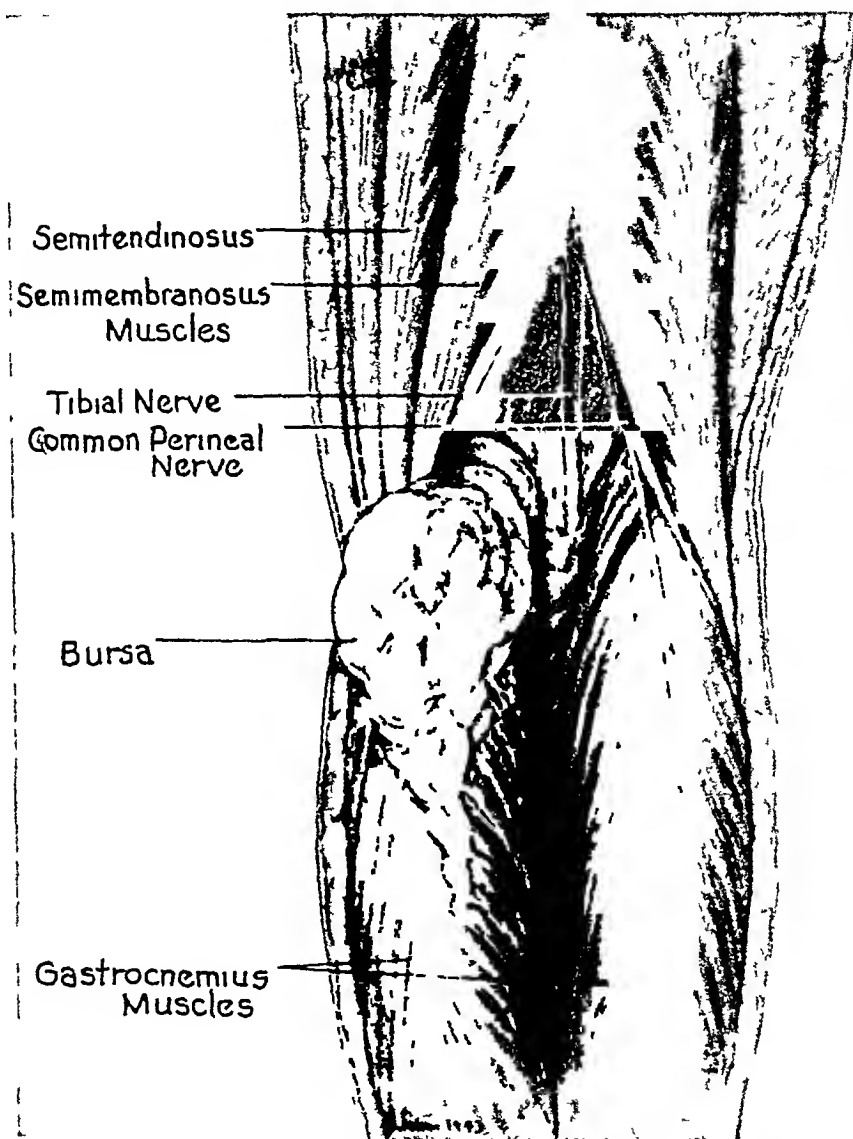


FIG. 4—Synovial cysts of the popliteal space due to hyperplasia of the semimembranosus bursa. Note that the character of the cyst wall is similar to that shown in Figure 3.

plaster encasement, the knee in full extension, this discomfort was greatly alleviated, the degree of swelling in the joint was less pronounced, while the return of normal muscle function in the extremity was not delayed because of the active exercises instituted, namely, repeated contraction of the quadriceps muscle, and also lifting the extremity clear of the bed when lying supine. Following removal of the splint, progressively more active muscular exercises are encouraged, and the patient is then allowed up and progressive

weight-bearing is instituted. In the case of older patients, or those with relatively poor muscles initial weight-bearing is carried out with the aid of crutches, and these are also employed when the patient has had a considerable operative reaction in the knee joint. The average period of hospitalization is 18 days.

RESULTS

Thirty-four patients with synovial cysts of the popliteal space have been operated upon. In one instance the cyst was bilateral, making a total of 35 cysts explored and removed. In 22 cases the cyst was the result of posterior herniation of the knee joint, while in the remaining 13 the cyst was due to enlargement and distention of the semimembranosus bursa. With the exception of one patient, there are no recurrences. This man now exhibits, three years after operation, a fullness in the popliteal space but in no sense a round, ball-like mass such as was present before surgery. He has refused reoperation because the knee does not bother him enough to warrant it. All patients in this series exhibit the same range of motion as was present before operation and have returned to their previous occupations. Swelling of the knee or lower leg region is absent.

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HEMANGIO-ENDOTHELIOMA A TUMOR OF BLOOD VESSELS FEATURING VASCULAR ENDOTHELIAL CELLS

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ACCORDING to Shaw (1928) blood vessels are formed in the embryo from angioblastic endothelial cells developing in the vascular layer of the mesenchyme. These cells first form solid cords and islands, lumens then appear in them and, finally the isolated structures unite to form continuous tubes. If some of these structures fail to unite and remain segregated, they may grow independently and form hemangiomas which may subsequently unite with normal blood vessels or remain separated from them. They may remain as simple capillary tubes consisting of endothelial lining cells surrounded by a delicate reticulin framework or have, in addition, other cells normally associated with blood vessels such as smooth muscle cells and pericytes, and also, on occasion, other tissues such as fat smooth muscle, myxomatous tissue bone, mature and immature red and white blood cells and perhaps other cells which may be derived from mesenchyme.

This accounts for the focal origin of a large majority of vascular tumors but it does not account for all, nor does it explain the spread and infiltrative growth of any of these tumors after they have once formed. This takes place by a process similar to the formation of capillaries in granulation tissue which occurs by the sprouting of endothelial cells from preexisting capillaries forming first a solid cord which secondarily becomes canalized. It seems probable that the malignant tumors in this series, which appeared in traumatized areas (Cases 8 and 14), must have developed in this fashion from the capillaries of granulation tissue. Probably all of the malignant tumors exhibit this type of growth in their infiltrative growth.

These methods of development make possible a very wide variety of gross and microscopic forms which have been endlessly described and named by pathologists, dermatologists neurologists and many others. It often leads to the formation of multiple tumors. Usually such tumors even if they appear successively and grow to a large size, are not suspected of being malignant growths but a few cases have been recorded whose behavior has raised this question. In some, such as the cases of Glogengiesser (1939), Rabson (1938), Weiss (1911) in humans, and Sal (1931) in chickens, growth of vascular and related tissues occurred in widespread areas, as if it were due to a profound and perhaps systemic disturbance of the vascular system akin to von Recklinghausen's disease in the nervous system. If Kaposi's disease is neoplastic it probably belongs to this group. In another group of cases, what have been described as benign hemangiomas have developed in one area

with the subsequent appearance of hemangiomas or hemangio-endotheliomas in other areas, as if they were metastases. This phenomenon has given rise to the term benign metastasizing hemangioma. The writer has never observed such an anomaly in his own material, and questions its occurrence. The subject will be discussed later in this paper.

In spite of the fact that blood vessels are ubiquitous, and benign vascular tumors exceedingly common, malignant tumors of blood vessels are exceedingly rare. Just how many of them have been recorded is impossible to say because many tumors have been reported as such with insufficient or obvi-



FIG 1—Case 1. Hemangio endothelioma of the mammary gland in a 19 year old girl, 14 months after onset, just before it was removed. The enormously enlarged bluish, turgid right breast weighed 1647 Gm., and contained a liter of blood.

ously erroneous data. After reading reports of 118 cases labelled with some name suggestive of a malignant vascular tumor, the writer felt compelled to reject 41, or 35 per cent of them, either because there was an inadequate or no histologic report, or because in his opinion, the illustrations and text described a tumor of some other kind.

There are certainly two and probably three, malignant vascular tumors all characterized by the formation of vascular tubes but with different cells playing a dominant role in tumor growth. Attention has already been called to the group featuring the pericyte (Murray and Stout, 1942, Stout and Murray, 1942) for which the name hemangio-pericytoma has been suggested. This group includes the glomus tumors, and the vast majority of them are benign. However, two cases have shown aggressive infiltrative growth, and at least one other is known to have metastasized—establishing the existence of a malignant variant.

Since smooth muscle forms an important part of many blood vessels, one might expect to find a vascular form of leiomyosarcoma. There is a benign

vascular leiomyoma (Stout, 1937, 1938), hence from the theoretical viewpoint, there is no reason why there should not also be a malignant form of this tumor. The evidence that such a neoplastic type exists is scanty. Fourmestiaux and Foulon (1930), Grandclaude, Lambert and Driessens (1933), Leuret *et al* (1930), and König (1921), believe that such tumors occur. The case reported by Leuret, and his associates, seems to have been composed of both atypical smooth muscle and many vessels, sometimes with heaped-up irregular endothelia and may, indeed, be truly compounded of both of these elements. It would be preferable to obtain further confirmation from others before accepting this as a definite type and not just a sport. This writer has not encountered such a tumor.

The third group is much better known and contains the majority of the malignant vascular tumors. It also forms vascular tubes but the important cell responsible for its aggressive growth and metastases is the endothelial cell. Because of this, it is best called by the name hemangio-endothelioma, devised by Mallory (1908), which is properly descriptive and has the added advantage of familiarity.

The writer has had the good fortune of assembling 18 such tumors from various sources, which he is permitted to present in a group through the generosity of several different pathologists and surgeons. Such a collection affords a better opportunity to study the characteristics and peculiarities of this tumor type than can be gained by attempting to analyze and collate the literature, for the reasons already indicated. The writer will base most of his remarks upon this material and only supplement it when necessary from the reports of others.

Eleven of the patients here reported were females and seven males. Three of them were colored. The age at onset varied from birth to 66 years, nine were less than 30 years of age but six were over 50 years. A tumor of the popliteal space (Case 14) and the one in the erector spinae muscles (Case 8) developed in traumatized areas.

The distribution of the primary lesions is shown in Table I.

TABLE I
PRIMARY SITES OF HEMANGIO-ENDOTHELIOMAS

Mammary gland	3	Pleura	1	Skin and subcutaneous tissues } 6
Liver	2	Uterus	1	
Bones	2	Orbit	1	
Striated muscles	2			

The majority of reported cases have been in the spleen, the liver, the bones, or in the skin and subcutaneous tissues. In acceptable reports of others can be found the following additional primary sites mentioned: Tonsil (de Bary, 1935), stomach (Sherill and Graves, 1915), intestine (Magnusson, 1934), omentum (Ransom and Samson, 1934), retroperitoneal space (Beitzke, 1932, Leubner, 1935, Cannata 1931), lung (Hall, 1935, Plaut 1930), mediastinum (Shennan 1914), heart (Gross and Englehart, 1937, Hewer and Kemp, 1936), pericardium (Scheidegger, 1937), ovary (Sovak

and Carabba, 1931), corpora cavernosa (Foulds and Flett, 1938), central nervous system (Turner and Kernohan, 1941)

The malignant nature of these tumors is fully confirmed by the outcome of the cases in this group. Of the 18 patients, ten are known to have died with metastases, one was last seen with local persistence of disease, one had had nine operations for local reappearances and was not followed after the

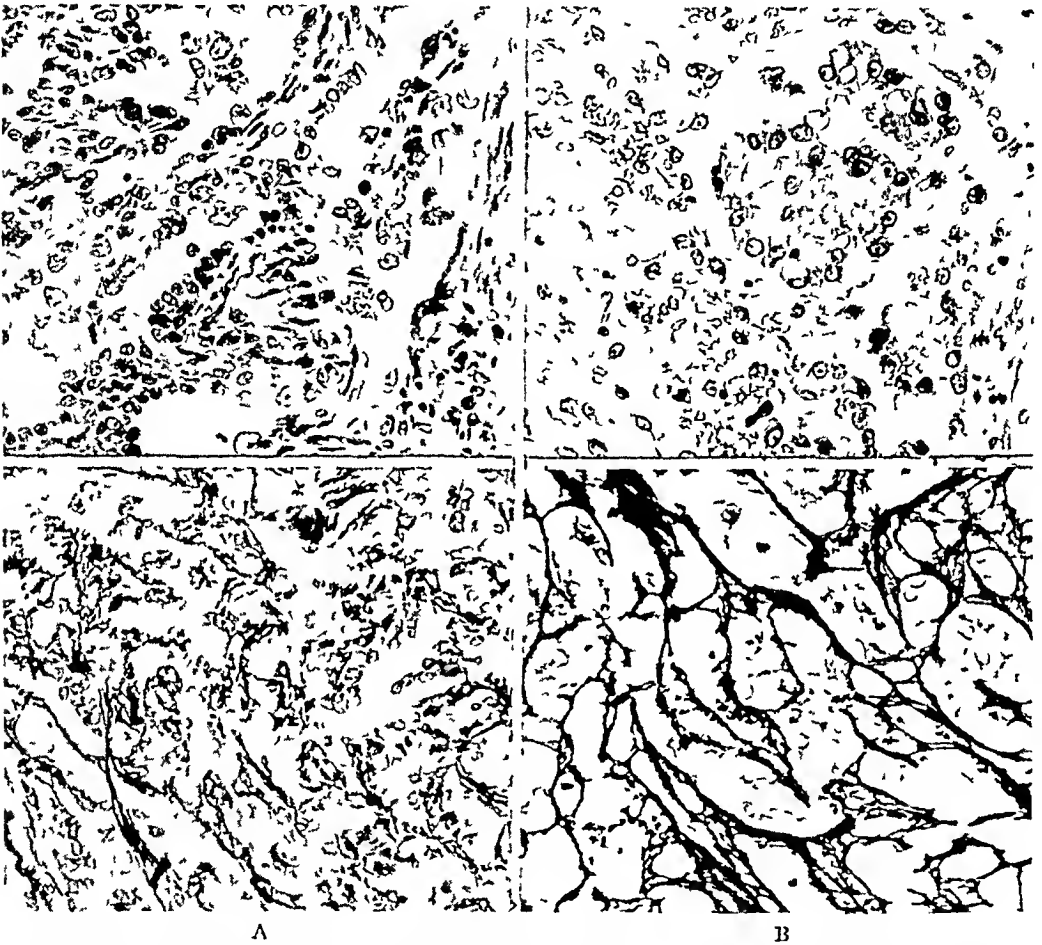


FIG. 2—Case 13. A (left) Hemangioendothelioma of supraclavicular region. Anastomosing vascular channels lined by heaped up rounded atypical endothelia. Silver reticulum stain below outlines the vascular tubes.

Case 14. B (right) Hemangioendothelioma of popliteal region. Poorly defined vascular channels lined by swollen polygonal endothelia are shown above while below the silver reticulum stain accentuates the vessels by blackening their supportive framework (see Fig. 9). ($\times 525$ reduced)

last operation, three patients are without evidence of tumor 8, 12 and 30 months after removal, two were not followed, and only one is known to be well five years and two months after excision of a popliteal tumor.

As in other malignant tumors, the course of the disease is sometimes fulminating, as shown by Case 2, the 65-year-old woman, who was dead eight weeks after she first noticed a growth in her breast, and sometimes exceedingly protracted, as exemplified by Case 16, who during the first 19 years of her life had had a persistently growing tumor of the upper eyelid which constantly recurred in spite of eight attempts to remove it (Figs. 10 and 5 B).

The vascular nature of these tumors can generally be appreciated when one approaches them, and they have a tendency to bleed either into themselves or externally if they penetrate through a body surface. An example of the former condition is furnished by Case 1, the 19-year-old girl, with a tumor in the mammary gland which contained a liter of blood in it (Fig 1). This bleeding was associated not only with a severe anemia but a purpura, with platelets averaging only 51,000. An example of surface bleeding is furnished by the uterine tumor (Case 10) which bled with increasing severity over a two-year period. On the other hand, Case 18 gave no evidence of its vascular composition even when excised, and only microscopic examination revealed its true nature. It developed in the eyebrow of a three-months-old boy, and was mistaken for a dermoid cyst.

Great vascularity and hemorrhages, while they may suggest a tumor of blood vessels, are not in themselves sufficient to prove that a neoplasm is indeed a malignant tumor of vascular elements. Both Molotkoff, (1933) and Ogilvie and MacKenzie (1936), have pointed out that chorio-epithelioma can be confused with blood vessel tumors and every experienced pathologist will recall extremely vascular hemorrhagic malignant tumors of other types. The diagnosis must, therefore, rest upon the histologic characteristics. These display themselves in a variable fashion and require presentation in some detail.

There are two features of the growth of hemangio-endothelioma which are striking and uniformly present in all true tumors of this kind, although they are sometimes masked and require differential staining clearly to demonstrate them. These are: First the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane, and second the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose. No tumor should be considered a hemangio-endothelioma unless these criteria are both present. The variations found are due to the marked variability in the number, shape, size and tinctorial peculiarities of the malignant endothelia. They may be irregularly rounded or polygonal (Figs 2 A and B) or they may maintain an elongated shape (Figs 3 and 4), they may form only a single continuous layer (Figs 3 B and C) or they may become heaped up and more or less fill the lumen (Fig 5 A). Usually they remain within the vascular tubes but occasionally they grow outside of it and form solid sheets of cells (Figs 4 A and B). Whatever their shape, the tumor cells always differ from the endothelial cells of simple benign angiomas and normal blood vessels although occasionally the blood vessels which are formed in the process of organization of a thrombus may simulate their appearance. It is usually easy to perceive that a tumor is composed of vascular tubes which tend to anastomose and are lined by atypical endothelia. When there is doubt about these things with ordinary stains the relationships can be clarified by the use of a silver reticulin stain. This will cause the tubes

to stand out in sharp relief because each one, even in the most malignant tumor, has a delicate fibrous supporting framework and the silver brings out a distinctive pattern (Figs 2, 3, 4 and 5). This pattern will be revealed with silver even when, with other stains, it is entirely obscured by an overgrowth of cells (Fig 4 B). When ordinary stains make it impossible to decide



FIG 3—Case 10. A (upper left) Hemangioendothelioma of uterus. Infiltrative extension of anastomosing blood vessels lined with bizarre elongated endothelia through the myometrium. Case 6. B (lower left) Hemangioendothelioma of tibia. Proliferation of anastomosing capillaries lined with hyperchromatic endothelia in the marrow. Case 3. C (right) Hemangioendothelioma of breast. Complex formation of vascular channels lined with hyperchromatic endothelia. The Laidlaw silver reticulum stain shown below accentuates the vascular pattern ($\times 525$ reduced).

whether cells are grouped inside or outside of a vessel wall, and so to determine whether one is dealing with endothelia or pericytes, silver staining of the vascular reticulum sheath shows the exact relationship of the cells beyond peradventure (Fig 5 A).

If one tries to group these tumors in order to give them descriptive subtitles, one encounters almost insuperable difficulties, for the cellular appearance and make-up not only may vary in different parts of the same tumor but also in its recurrent or metastatic manifestations. Some features however, deserve special emphasis.

One variety of this tumor manifests a certain degree of constancy in its form. It seems to grow especially in infants, and there are two examples of it represented in the present series (Cases 17 and 18), both of which closely resemble one another in every way. These tumors differ from all of the others in that they both maintain a uniform histologic appearance throughout (Fig 5 A) so that the illustration furnishes an accurate picture. They are composed of closely packed capillaries with heaped up endothelia and a tendency to anastomose so that they are by definition hemangio-endotheliomas, but growth although rapid, is orderly and neither has recurred nor metastasized in the short space of time they have been followed. Nevertheless, one must not assume that this special form always pursues such a benign course. The kindness of Dr Beryl Paige, Pathologist of the Babies Hospital, has enabled the writer to review the slides of the case of a female baby dying in its fifth month which was reported by the late Dr Martha Wollstein (1931) as a "malignant hemangioma of the lung with multiple visceral foci." In this case there were many tumors in skin and viscera, the majority of which were exactly similar to the two tumors here reported, while the rest were simple capillary or cavernous hemangiomas. It is really impossible to decide whether these tumors are multiple independent growths, as seems probable, or whether some of them are metastases. The question of metastasis of a simple hemangioma does not here arise for the growths are definitely hemangio-endotheliomas.

At this point, it seems pertinent to debate the question of the so-called benign metastasizing hemangiomas. The writer reread the published reports of some of these cases in an effort to determine whether or not he could agree with the authors that the tumors were simple hemangiomas and that they metastasized. The cases of Langhans (1879), Borimann (1907), Shennan (1914), Wright (1928), and Surala and Naatanen (1940), all show atypical endothelia and very free vascular anastomoses, which bring them definitely into the class of hemangio-endothelioma. The cases of Weiss (1911), Konjetzny (1912) and Ewing (1928), are not illustrated with photomicrographs so that the reader cannot judge for himself. Stamm's (1891) thesis was not available.

Robinson and Castleman (1936) reported that the primary tumor in their case was a simple hemangioma, while the metastases were angiosarcomatous. Their illustrations support this contention. It seemed important to review this case to determine whether or not the whole primary tumor appeared like the illustration. Dr Castleman was kind enough to permit me to examine the original microscopic preparations. They show that in the primary growth there are some areas with extremely free-sprouting and anastomosis of capillaries which are lined with prominent darkly stained endothelia varying in relative size. Thus this case also shows features which lead me to classify it as hemangio-endothelioma and not simple benign hemangioma.

In the present group of tumors, Case 1, which has been reported previously

with illustrations, by Hill and Stout (1942, Case 25), showed in the primary tumor the formation of a meshwork of anastomosing capillaries lined with deeply stained swollen endothelia, which resemble Robinson and Castleman's tumor and that of Boirrmann, and are like Case 3 shown here in Figure 3 C. Such formations do not occur in simple nonmalignant hemangiomas. The picture may be reproduced occasionally in the very rapid formation of capil-

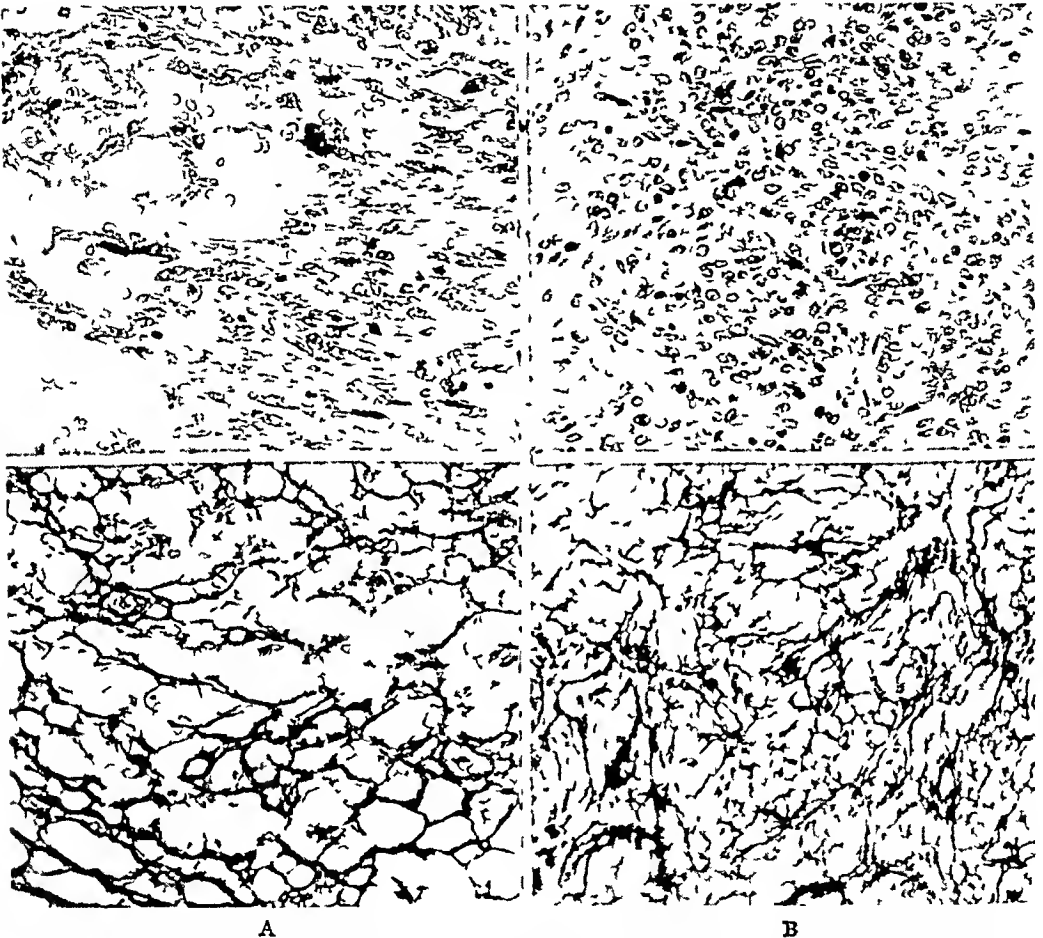


FIG 4—Case 8. A (left) Hemangioendothelioma of erector spinae muscle. Above, the vascular pattern is partly obscured by the sheet like proliferation of elongated endothelia, but the Laidlaw silver reticulum stain, below, demonstrates its presence.

Case 9. B (right) Hemangioendothelioma of calf muscles. The endothelia of this tumor form solid cords of cells coursing in various directions. Laidlaw's silver reticulum stain, below, brings out the vascular pattern (see Figs 6 and 7). (X525 reduced)

laries which can take place in the organization of intravascular thrombi. But here the growth is strictly limited to the thrombus and never invades surrounding tissues. This comparison emphasizes the fact that in malignant vascular tumors growth takes place by sprouting in the fashion characteristic of the formation of vessels in granulation tissue and not in the way blood vessels are developed in the primitive mesenchyme of the embryo.

Thus, the writer has not been able to find any case which, to him, offers incontrovertible proof of the existence of such an anomaly as a benign metastasizing hemangioma and he, therefore, doubts its existence.

One tumor (Case 9) in this series differs from all the others because the whole tumor is overgrown with elongated cells generally arranged in slender cords which are usually solid but sometimes have a core of red blood cells. In addition, capillaries lined with normal endothelia are frequent in some areas. Laidlaw's silver reticulin stain shows a vague tubular arrangement of reticulin corresponding with the solid cords of cells (Fig. 4 B). Grossly this tumor was extremely vascular and hemorrhagic (Fig. 7). The morphologic features of this tumor alone would hardly warrant its inclusion in the group of hemangio-endotheliomas. It seems proper to do so, however, because explanation *in vitro* demonstrated that the tumor cells had the characteristics of endothelia. Details are reported in a separate communication (Murray and Stout, 1943).

In all of the tumors here described, and in acceptable previously reported cases, the tumor cells appear as variously illustrated in this paper. There are a few tumors of bone called angio-endotheliomas which have cells of a different aspect. These demand separate discussion.

On page 362 of the 4th Edition of Ewing's "Neoplastic Diseases" there appears an illustration (Fig. 133) labelled "Structure of angio-endothelioma of bone." It shows large clear cells with small nuclei in alveolar arrangement with red blood cells in the lumens. In the text reference is made to a number of the older surgeons and pathologists who described similar bulky lesions in bones, which they considered primary vascular endotheliomas. Ewing says that he has seen three such cases, but in a final paragraph he warns that such tumors may be confused with metastases from primary growths elsewhere. Thomas (1942), in his paper dealing with vascular tumors of bone, has apparently been influenced by Ewing, for he includes cases which he calls angio-endothelioma. One of them is illustrated and is Bone Sarcoma Registry Case 2156. It formed a bulky tumor in the humerus. Death followed six months after amputation, apparently from heart disease, and there was no autopsy. The photomicrograph shows a tumor exactly like that illustrated by Ewing.

If these tumors are truly hemangio-endotheliomas they differ histologically from any others in other parts of the body, and must be a variety peculiar to bone. They can be explained more easily as metastases. The histologic structure described and illustrated is exactly like hypernephroid carcinoma. Red blood cells in the lumens of the tubules lined by the characteristic clear cells is not an uncommon finding in the primary kidney tumors. Moreover, a solitary metastasis to bone from an occult hypernephroid carcinoma is a well recognized phenomenon. For these reasons it seems improper to accept such cases as hemangio-endotheliomas or, indeed, as vascular tumors at all.

CASE REPORTS

BREAST

Case 1—J. M., white female, age 19

Slightly bluish lumps in the right breast of three months' duration were treated

for six months with estradiol benzoate without avail. When biopsy showed what was wrongly interpreted as a capillary hemangioma this was stopped and four months later quinine and urethane were injected into the constantly enlarging breast. Five months after biopsy the enormously enlarged, turgid, discolored breast was removed by Dr D C Bull (Fig 1). It weighed 1647 Gm and contained a liter of blood. Two months later metastases began to appear, first in the abdominal wall and later in the humerus, scapula and lungs. Before mastectomy the platelets were low and now

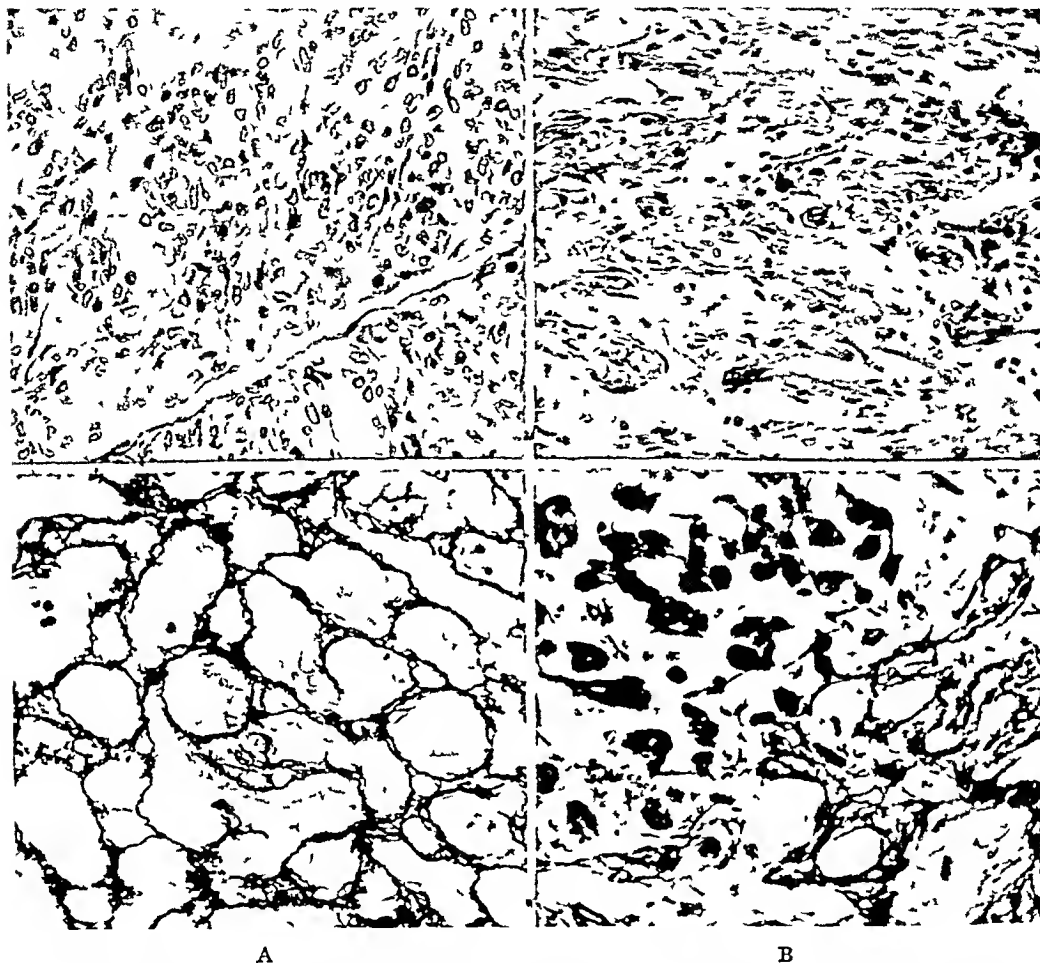


FIG 5—Case 17. A (left) Hemangio endothelioma of scalp. Above are shown the vessels with rounded cells surrounding their lumens. One can only be certain that all the encompassing cells are endothelia by using silver to outline the vascular framework, as shown below.

Case 16. B (right) Hemangio endothelioma of eyelid. Above, is shown the anastomosing vascular channels lined by elongated hyperchromatic endothelia. Some of these are encased by thick collagenous sheaths as shown by the silver stain below (see Fig 10) ($\times 525$ reduced).

they dropped to 51,000, and ecchymoses appeared on the legs. Three months after mastectomy she died, with symptoms of abdominal hemorrhage.

The breast was honeycombed with blood-filled cavities of all sizes, and these showed a proliferation of rounded and flattened malignant endothelia sometimes heaped up and sometimes in a single layer, quite comparable to the tumor shown in Figure 2 A. The primary growth showed freely anastomosing capillaries lined by swollen elongated endothelia, comparable to Figure 3 C (Hill and Stout Sarcoma of the Breast Case 25, illustrated).

Case 2—J M., white female, age 65

A five-centimeter nodule lateral to the nipple in the right breast with a reddish-

purple hue to the elevated overlying skin and a suggestion of pigskin effect. Radical mastectomy was performed two weeks after onset, and the firm, grayish-white mass was speckled with areas of hemorrhage and yellow foci. There were no axillary metastases found. Microscopically, the growth resembled Case 1. One month later there were recurrences in the scar and lung metastases. Irradiation was without effect, and two months after onset the patient was dead. (Case of Drs W C Seelye and J P Beck, Worcester, Mass. Reported by Hill and Stout. Sarcoma of the Breast, with illustration)

Case 3—A P, white female, age 68

Pain in the right breast of two years' duration and a lump which, after a blow some months before, became black and blue and began rapidly to increase in size. It was said to be the size of an orange when simple mastectomy was performed. One month after mastectomy there was a recurrence in the scar, from which blood was aspirated. Three months after mastectomy there were metastases in both lungs and the right ischium. Numerous skin metastases next appeared over opposite breast and forehead. In spite of irradiation therapy with roentgen-ray and radium she died four months after operation. The breast tumor, examined by Dr A O Severance, was 7 x 4.5 x 3.5 cm, and grossly suggested a hemorrhagic fat necrosis. He correctly diagnosed it as malignant hemangio-endothelioma. It closely resembled the two preceding cases (Fig 3 C). (Case of Drs C S Venable, D Jackson, and A O Severance, San Antonio, Texas)

LIVER

Case 4—Autopsy 11340 M B, colored male, age 54

This syphilitic patient had been under treatment for diabetes for a year. Seven weeks before death he suffered from abdominal cramps, profuse diarrhea and bloody ascites. He failed rapidly, and died without remission of symptoms. At necropsy, the liver weighed 2740 Gm, and measured 29 x 13 x 23 cm. It was filled with large hemorrhagic nodules and smaller hard yellowish-white ones. Metastases were found in pancreas, kidneys, right suprarenal, spleen, diaphragm, lungs, peritoneum, omentum, abdominal skin and abdominal lymph nodes. Microscopically, the tumor is composed of multiple anastomosing vascular tubes lined by large bizarre endothelia which are heaped up in many places. The multiplication of these cells is so great it obscures the tube formation in some areas but its presence is revealed by the silver reticulin stain. The abdominal skin nodules were found around the punctures of the paracentesis needle and may represent tumor implants. (From the Pathology Laboratory of the Presbyterian Hospital. Dr J W Jobling, Director)

Case 5—Path 12177 A C, male, age 52

Symptoms began with a dragging pain in the right flank one year before death. It gradually became worse, with radiation to epigastrium, loss of weight, darkening of skin, weakness, dizziness and dyspnea. Except for a large liver, no definite findings were recorded. Following cystoscopy, he developed acute uremia and died in a few days. At necropsy, the liver weighed 3020 Gm, and measured 31 x 19 x 10 cm. It contained multiple large and small nodules of yellowish-red hue, found chiefly in the right lobe. The largest was three centimeters in diameter. Metastases were found in the heart and lungs. The tumor is made up of vascular tubes outlined by reticulin fibers, lined with large, swollen, elongated endothelia of bizarre appearance and variable size and shape, which are not heaped up (similar to Fig 3 A). (From the Pathology Laboratory of the Presbyterian Hospital. Dr J W Jobling, Director)

BONES

Case 6—L D, female, age 60±

Four months before operation pain began in the region of the left external malleolus

and was soon followed by swelling in the lower leg and ankle but not in the foot. No history of trauma. Roentgenograms showed evidence of a destructive central lesion in the lower ends of the tibia and fibula, with widening of the bones. When the marrow cavities of the lower ends of the tibia and fibula were exposed they were filled with a very vascular tissue which looked like sponge rubber. This was curetted out. The wound was packed open because of oozing, with subsequent secondary closure and

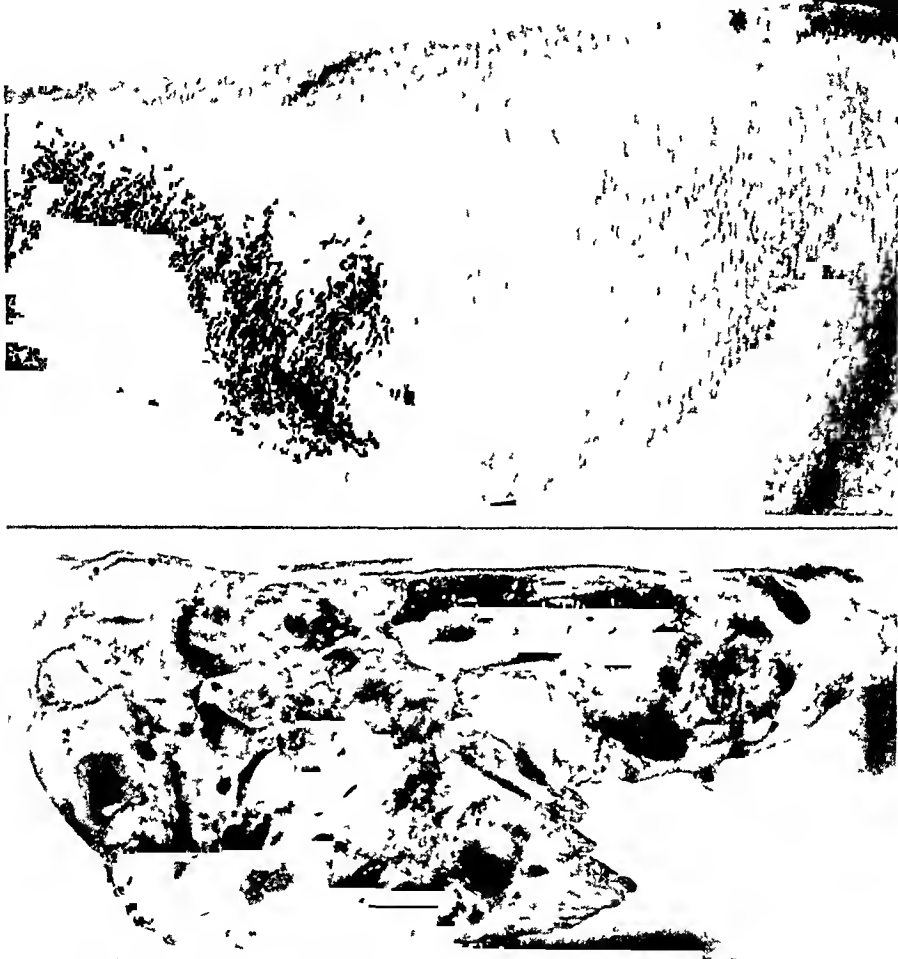


FIG 6—Case 9. Hemangio endothelioma of flexor longus digitorum and flexor longus hallucis muscles in the left calf of a 28 year old colored male. It was 11.5 cm larger than the right calf (see Figs 4B and 7).

FIG 7—Case 9. Section of the large tumor showing many hemorrhages, vascular spaces and areas of degeneration (see Figs 4B and 6).

good healing. Three months after the operation roentgenograms showed what appeared to be an extension of the process in the tibia and fibula and similar areas of rarefaction in all the tarsal and metatarsal bones and a possible area of involvement in the great trochanter of the femur of the same side. She was known to have been alive ten months after operation, but the final result is unknown. The tumor is composed of great numbers of small capillaries which anastomose freely and are lined by prominent hyperchromatic endothelia. These are all elongated and frequently fill and obliterate the lumen. The stroma is often filled with red blood cells. The bony trabeculae show pressure atrophy (Fig 3 B). (Case of Drs H. W. Cave, surgeon, and W. Brandes, pathologist of the Roosevelt Hospital, N. Y.)

Case 7—Young female (20±)

The history of this tumor is not available. It is known to be primary in a rib. It metastasized widely, and killed her in two or three years. The case was studied by Dr H E MacMahon, in the Laboratory of Pathology, Tufts College Medical School, who permits its inclusion in this group. Dr Frederic Parker called the case to my attention. Histologically, the tumor shows great variability, in some areas the vascular tubes are lined with elongated cells, elsewhere the cells are rounded and heaped-up, and, finally, overproduction of tumor cells in solid masses obscures the vascular tubes.

MUSCLES

Case 8—J P, male, age 14

Eight months before operation this boy fell, striking his side and back. There was not much pain at the time but one week later dull aching in the interscapular region began. It persisted and, finally, a deep mass was felt. Roentgenograms were negative. It was first explored by Dr W Darrach, and found to lie in the right erector spinae group of muscles, with its upper end at the level of the spine of T 6. It was dark purple, rubbery, not encapsulated, and about five centimeters in diameter. A biopsy showed that the tumor was malignant, and five days later the mass was excised with the surrounding muscles, but some of it was left behind in the sixth right intercostal muscle. In four months there were evidences of lung metastases and symptoms of paraplegia. Death occurred seven months after operation. This tumor is composed of many vascular spaces outlined by reticulin fibers and lined with both rounded and elongated bizarre endothelia. The vessels are often obscured by an overgrowth of these elongated cells which appear in solid sheets (Fig 4 A).

Case 9—M W, colored male, age 28

The growth first appeared unexpectedly as a marble-sized lump in the left calf, three years before operation. It was stationary until nine months before when the calf began to swell. Four months before aspiration yielded only blood. Examination showed a diffuse enlargement of the left calf which measured 47.5 cm in circumference, while the right was only 36 cm (Fig 6). When a frozen-section showed a malignant tumor, amputation through the middle third of the thigh was performed by Dr C D Haagensen. Eight months later there was no evidence of return. The tumor measured 16 x 13.5 x 6 cm, was exceedingly vascular, with large spaces filled with black, viscid bloody fluid, and lay with the flexor digitorum longus and flexor hallucis longus muscles, from which it had apparently arisen and invaded the overlying soleus and peroneus brevis muscles (Fig 7). The microscopic picture in this tumor is obscured because of the great degree of overgrowth of elongated endothelia which form apparently solid sheets and cords, with spaces containing red blood cells scattered among them. The Laidlaw silver reticulin stain outlines the vascular tubes (Fig 4 B), and the diagnosis was made certain by the growth of endothelia from tumor explants *in vitro*, by Dr Margaret Murray. Details will be given in a separate communication.

UTERUS

Case 10—A M S, married female, age 28

Thirty-one months before operation she began to have gradually increasing menorrhagia. Seven months before she bled daily for one month. A curettage showed that most of the endometrium was replaced by capillaries, and it was supposed that she had a hemangioma. Bleeding continued, and a month later a second curettage showed persistence of the vascular tumor. During all this time she suffered from attacks of cramping abdominal pain. Just before operation the temperature was 100° F, pulse 140, vaginal bleeding profuse and there was pain in the chest and cough. At operation the uterus was soft and enlarged to the size of a three months' pregnancy.

Hemorrhagic implants were found on the lower sigmoid and in the cul-de-sac of Douglas. A supravaginal hysterectomy, right salpingo-oophorectomy, appendectomy, and biopsy of sigmoid was performed. When the uterus was opened, a reddish, friable tumor mass was found in the endometrium of the fundus. It penetrated the myometrium. Several other similar, but smaller foci were found in the left cornu and on the posterior wall. Nine months later, metastases were found in the left scapula and still later in both lungs, peritoneum and pelvic bones. She became too anemic to tolerate roentgenotherapy. She died 14 months after operation. This tumor throughout its course shows the same histologic picture. It is composed of capillaries lined by

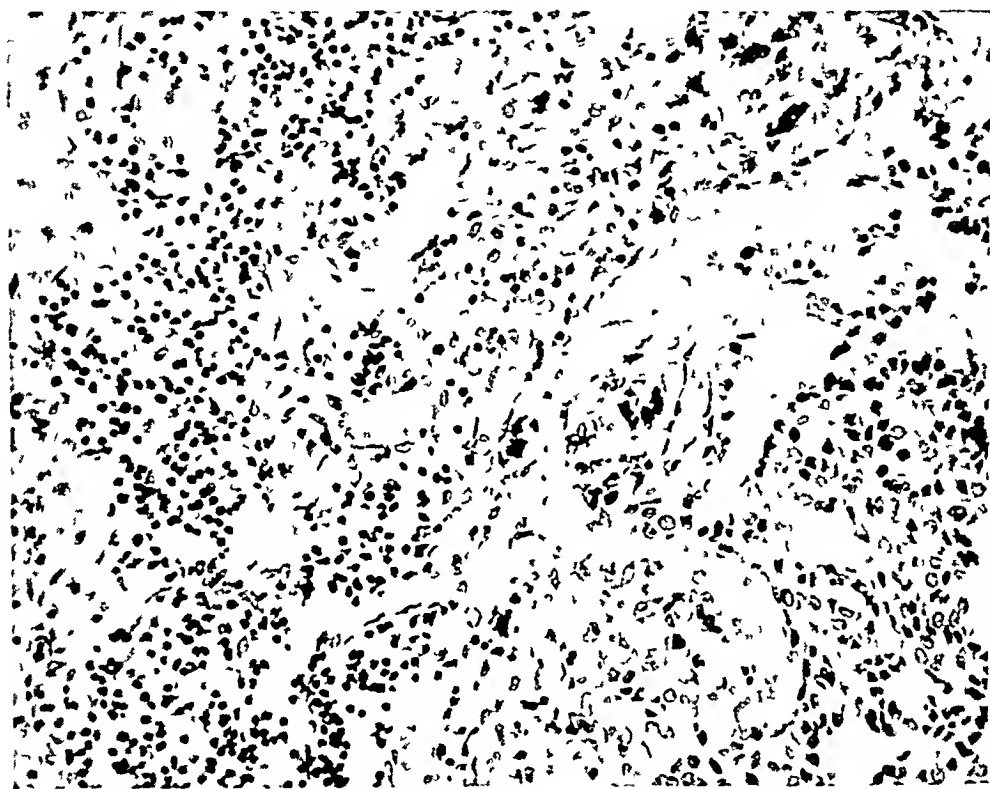


FIG 8—Case 11 Hemangioendothelioma of pleura. Metastasis in a hilar lymph node. Capsule and marginal sinus at left. Anastomosing tumor vessels lined with bizarre endothelium at right.

swollen, elongated, hyperchromatic bizarre endothelia showing great variation in size and frequent mitoses. The cells are almost always in a single layer and there is little tendency to heap-up or invade outside the vessel wall. The tumor shows marked infiltrative tendencies (Fig 3 A). (This case was treated in Sloane Hospital, N. Y. by Dr. B. P. Watson, Director, and is included with his permission.)

PLEURA

Case 11—T. T., male, aged 61

Eight months before death, pains began in left lower chest, followed by night sweats, weakness and hemoptysis. Two months before death, he entered the hospital and bloody fluid was repeatedly removed from the left pleural cavity. It was felt that he had a cancer of the lung. After a progressive downhill course he died at the Lincoln Hospital, and was autopsied by Major Chester R. Brown, N. Y., who permits me to include this case. The entire left pleura, both visceral and parietal, was markedly thickened by the hemorrhagic tumor. Metastases were found in the hilar lymph nodes (Fig 9) and the left lung, and the diaphragm was invaded. In

addition, simple cavernous hemangiomas were found in the diaphragm. This tumor consists, basically, of freely anastomosing vascular tubes lined by atypical endothelia which sometimes are rounded and heaped-up and sometimes flattened, forming a one layer membrane (Fig 8)

ORBIT

Case 12—I P, female, age 40

She suffered for two years from swelling of the left upper eyelid, with proptosis and double vision during the last three months. Roentgenograms showed an enlargement of the left orbit. At operation, by Dr G M Bruce, a firm mass extended along the roof on the nasal side, from the apex nearly to the anterior orbital margin. Although adherent, it was excised, and measured two centimeters in length. Following this she got a complete paralytic ptosis. Eighteen months later an attempt to correct this by operation failed because of tumor recurrence. A second attempt to excise this was made three years after the first operation. This failed because the growth now infiltrated the medial rectus muscle and the optic nerve. When last seen, six years after the first operation, the globe was fixed and immobile and the ptosis persisted. The tumor appears the same in both manifestations. It consists of freely anastomosing vascular channels occasionally lined by swollen rounded heaped-up endothelia but often obscured by an overgrowth of elongated endothelia. (Case treated at the Institute of Ophthalmology, N Y, and included by permission of Dr J H Dunnington, Clinical Director)

SUBCUTANEOUS TISSUE AND SKIN

Case 13—W R, male, age 25

For two years there had been a swelling in the right supraclavicular fossa, which slowly increased in size, without symptoms, until three months before operation, when pain radiated from it down to the wrist. This disappeared in three weeks but tenderness remained. When examined it was five centimeters in diameter. At operation, the mass appeared like a dark red plum, and was very vascular. It was excised with an adjacent lymph node. When the nature of the growth was determined and direct invasion of the lymph node recorded, the lymph nodes of the right lower neck were removed. No metastases were found. Thirty-seven months after operation metastases appeared in both ischia, left pubis, L 2, L 4, sternum and 6th rib. These were treated by irradiation, with some improvement, so that the man could continue his work. Four years after operation there were lung metastases. He finally died, five years and two months after operation. There was no autopsy but biopsy of a rib confirmed the fact of metastasis. The tumor is made up of freely anastomosing vascular tubes sometimes lined by a single layer of prominent hyperchromatic, flattened endothelia but usually by rounded, swollen, heaped-up tumor cells of varying size (Fig 2 A). (Three months after the first operation the case was reported Dr J M Hanford)

Case 14—H G, colored female, age 49

She received a blow on the medial aspect of the left knee region two years before admission. This was immediately followed by ecchymosis. Two months later attacks of throbbing pain began and lasted for 16 months, when swelling began, and all symptoms grew worse. Examination showed a diffuse swelling of the posteromesial aspect of the left popliteal region. There were extensive varicosities in this extremity. The lesion was explored, and a large multilocular cystic cavity found containing from 300 to 400 cc of old blood. It was supposed to be a hematoma. The blood was evacuated and the wound closed. Later, it broke open again and drained foul-smelling bloody material, while the pain and swelling increased. Ten months later, at a second operation, by Dr A H Blakemore, a tumor eight centimeters in diameter was found. It was subcutaneous, sharply circumscribed and involved the deep fascia. It was excised

Sixty-seven months after excision there was no evidence of recurrence. The tumor consisted of a spongy mass of intercommunicating cavities filled with blood. A thick-walled vein entered the upper pole of the mass (Fig 9). Microscopically, this tumor shows numerous vascular tubes which often anastomose and are lined by heaped-up rounded endothelia. In many areas the endothelia have multiplied to such an extent that the lumens are solidly filled, and only the silver reticulin stain demonstrates them by accentuating the fibrous framework (Fig 2 B).

Case 15—Female, age 35

Seven months before operation several nodules developed in the scalp above the right ear. These were diagnosed as "cysts," and biopsy is said to have been taken but no report is available. Soon after, swellings appeared in the right neck. All were firm, circumscribed and somewhat painful and tender. A neck mass, midway between angle of jaw and clavicle, was explored. It was apparently encapsulated, 3 × 2 × 0.5



FIG 9—Case 14. Hemangioendothelioma of popliteal region. Cross section of the tumor tissue: its multiple cavities and the large vein which entered its upper pole shown at the right (see Fig 2B).

cm, and lay deep to, but not attached to, a branch of the cervical plexus. It was described as hemorrhagic. The patient was not followed. The tumor is composed of the usual widely anastomosing vascular spaces lined by rounded and polygonal cells, often heaped-up and sometimes forming papillary processes. (Case from the Hospital of the University of Pennsylvania. Reported by permission of Drs. Louis Kaplan, surgeon, and R. H. Horn, surgical pathologist.)

Case 16—S. K., female, age 17

Ever since birth there had been a "hemangioma" of the lateral aspect of the right upper eyelid. Prior to her first operation, at the Presbyterian Hospital, there had been six previous attempts at surgical removal, all of which failed. At this time, the tumor measured 15 × 10 × 5 mm. It was excised but promptly recurred (Fig 10). The 8th and 9th attempts were made, respectively, one year and 16 months after the 7th attempt. She was not followed after this last operation, when she was 20 years old. Grossly, the tumor was composed of firm hemorrhagic tissue. This tumor is made up in part of large, cavernous vascular spaces filled with blood and in part of a spongy meshwork of very freely anastomosing capillaries lined by swollen elongated endothelia frequently heaped-up in layers. The capillary sheaths are sometimes greatly thickened and seemingly hyalinized (Fig 5 B). (From the Ophthalmological Service of the Presbyterian Hospital. The late Dr. John M. Wheeler, surgeon.)

Case 17—W W, female, age 3 months

A red spot was present at birth in the skin of the right parietal region. It was one centimeter in diameter and increasing rapidly in size when it was excised. It lay in the skin and did not seem to have any deep connections. No recurrence after 30 months. The growth infiltrates the structures of the skin quite freely without destroying them. It consists of numerous closely placed blood vessels lined with heaped-up rounded endothelia, the most internal layer of which tend to be elongated. This makes it appear in ordinary stains as if the vessel is surrounded by pericytes. Because of this the tumor at first was called a hemangiopericytoma (Stout and Murray, 1942, Case 3). The silver reticulin stain shows that all of the cells are inside of the reticulin sheaths and are therefore, endothelia (Fig 5 A). (From the Nix Hospital, San Antonio, Texas. Drs L J Ross, surgeon, and A O Severance, pathologist)

Case 18—D R, male, age 11 months

When the child was three months old the mother noted a swelling over the inner angle of the left eyebrow. Slow increase to 25 mm diameter. It was subcutaneous, with normal overlying skin, and was mistaken for a dermoid cyst. No recurrence one year after excision. Microscopically the growth exactly resembles Case 17, except that it is subcutaneous instead of intradermal. Only a few of the vessels have visible lumens containing red blood cells, because multiplication of the endothelia has solidly filled them. The silver reticulin stain shows the true state of affairs. (Case from Babies Hospital, Dr B Paige, pathologist)

SUMMARY

Hemangio-endothelioma is the most common type of the malignant vascular tumors but, even so, it is a relatively rare neoplasm. It has a wide distribution in the various organs and tissues of the body, and may manifest itself at any age, although half of the cases occur in childhood or youth. Growth may be rapid or slow, and is infiltrative in character. When approached, the tumors are usually, but not always, obviously vascular with a tendency to bleed into themselves or from the surface. Metastasis is common and is generally through the blood stream although occasionally it progresses also through the lymphatics.

The tumors are made up of congeries of vascular tubes which have a marked tendency to anastomose and are lined with hyperchromatic atypical endothelial tumor cells. These may be of any shape and size. They may form a single layer, be heaped-up in several layers, or even multiply to such a degree that the vascular tubes are completely obscured, when ordinary stains are used, and can only surely be demonstrated by silver connective tissue impregnations. The same tumor may show two or more of these variations in the primary growth and the metastases. No tumor should be called a hemangio-endothelioma unless it fulfills these microscopic criteria and conversely, if a tumor does show these characteristics it should be recognized as a malignant or potentially malignant tumor. There is no such anomalous entity as a benign metastasizing hemangioma. Two other tumor forms especially have been confused with this one namely chorio-epithelioma and hypernephroid carcinoma. If the criteria already given are strictly applied one should be able to avoid this error. The hemangio-endothelioma of

infants apparently is better differentiated and probably less malignant, although it may kill by the multiplicity of its tumors, as occurred in Wollstein's case. The silver reticulin stain is of particular assistance in aiding one to distinguish hemangio-endothelioma from hemangiopericytoma, since endothelia are found inside and pericytes altogether outside the reticulin sheath of the vessels. Demonstration that tumor cells behave *in vitro* like endothelia provides further confirmatory evidence.



FIG. 10.—Case 16. Hemangio endothelioma of the right eyelid in an 18 year old girl. It was present at birth, and seven previous operations had failed to eradicate it (see Fig. 5B).

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VENOUS HEMANGIOMA OF SKELETAL MUSCLE

CASE REPORT

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VENOUS HEMANGIOMATA of skeletal muscle are not common. Jenkins and Delaney¹ reviewed 256 cases in 1932. Oughterson and Tennant,² in 1939, state that nearly 300 cases have appeared. Since that time seven other cases, three by Sorenson,³ and four by Fulton and Sosman⁴ have been reported. Several other titles of papers not available to the author are listed in The Quarterly Cumulative Index.

The lesion occurs nearly twice as often in the leg as in the arm, and has a predilection for larger muscles.² It is now generally conceded that the condition is congenital but the reason for the delay of onset of symptoms is not known. Trauma certainly is a dubious cause, appearing in only 17 per cent of cases.¹ The onset of symptoms in 79 per cent of cases is before the twentieth year, and in 94 per cent is before the thirtieth year.¹

The most frequent symptom was pain (70 per cent), but in only a few cases was this of paroxysmal character. Stout,⁵ in his analysis of 2080 tumors of skin and subcutaneous tissues found 20 instances (one per cent) in which paroxysmal pain was present—glomus tumors (angiomoneuromata) nine, leiomyomata, nine, hemangiomata, two, fibroma, keloid, sebaceous cyst, dermoid and neurofibroma, one each.

Deformity and impairment of function occurred in 50 of Jenkins and Delaney's 256 cases (23 per cent). A case similar to the one described herewith was reported by Josefsson⁶ in 1928.

Case Report—V U H No 107121 C N, white, male, age 16, was admitted to the hospital May 10, 1940. He had noted two years previously, without previous trauma, a slightly tender area on the posterior lateral surface of the right knee. Tenderness persisted and increased in severity. For the past year he had experienced pain in the region which in the beginning, was paroxysmal in character. He had



FIG 1—Showing flexion of knee plan for flexion contracture at ankle, and "tip toe" deformity.

noted nothing which would cause onset of pain. There was at no time evidence of inflammation or a palpable mass. During the past six months the pain had increased in severity and seemed to be made worse by standing. For the past three months it had been of such severity that he walked on the toe of his foot and used a "cane." In the past two months ambulation had become almost impossible, and he stated that he kept the leg flexed at the knee to alleviate the pain.

Physical examination revealed no abnormalities except of the right lower extremity. The patient lay in the bed with the right knee flexed. He was extremely apprehensive when the leg was approached, resisted all efforts to straighten it out, and cried out with pain frequently. There was a plantar flexion contracture at the ankle, and Figure 1 shows the "tip-toe" deformity. The right calf was three centimeters smaller than the left, but otherwise the extremities were symmetrical.

There was an area of excruciating tenderness over a three-centimeter area just

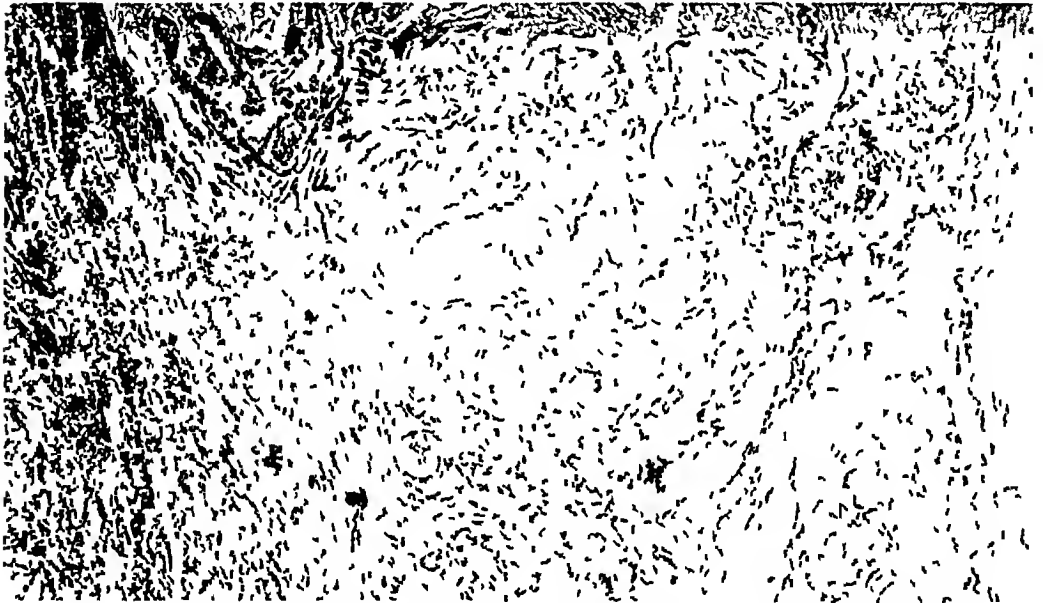


FIG. 2.—Showing infiltration of muscle by thick walled vessels, capillary and cavernous endothelial lined spaces, some containing blood, and some fibrosis.

behind and medial to the head of the fibula. This corresponded to the area of his pain. No palpable mass was present. Reflexes were normal and no sensory abnormalities, consistent with peripheral or central nervous system disease, were revealed. Skin temperatures of the two extremities were normal. Laboratory studies were not significant, and roentgenograms showed no abnormalities.

A diagnosis of glomus tumor was made and May 15, 1940, operation was performed by Dr. Barney Brooks. Under local anesthesia, an incision was made through skin, subcutaneous tissue and fascia over the point of maximum tenderness. Pressure on the lateral head of the gastrocnemius caused severe pain. On inspection of the deepest surface of the muscle, there was found an area, approximately 2 x 3 centimeters, having the appearance of cavernous hemangioma in which were flecks of yellowish tissue. No connection with the peroneal or posterior tibial nerves or vessels could be demonstrated. All the abnormal tissue was excised, after the administration of a general anesthetic.

After operation, traction was applied to the leg, and the foot was kept at right angles to the leg for six days. He began walking on the seventh day, with still considerable flexion deformity of the knee and with pain in the region of the wound. He was discharged on the ninth postoperative day, at which time he still experienced

pain exactly as before operation. He was examined two years and ten months after operation, at which time the only abnormality present was the defect in the medial aspect of the lateral head of the gastrocnemius muscle. The patient had not experienced any pain since discharge from the hospital. The flexion deformity of the knee gradually had disappeared during a period of three to four months.

Pathologic Report—Gross The specimen consists of a mass of skeletal muscle, 2 x 2 x 0.5 centimeters. At one end, and in the midportion, several bluish areas are present having the appearance of dilated blood vessels. No definite capsule is present.

Microscopically, sections show invasion of muscle by numerous blood vessels, varying in size from capillaries to fairly large arteries and veins. There is considerable smooth muscle between the vessels and in some areas epithelioid cells are present about the vessels. The striated muscle reveals considerable degeneration. There is a pacinian corpuscle near the area of invasion. *Pathologic Diagnosis* Glomus tumor.

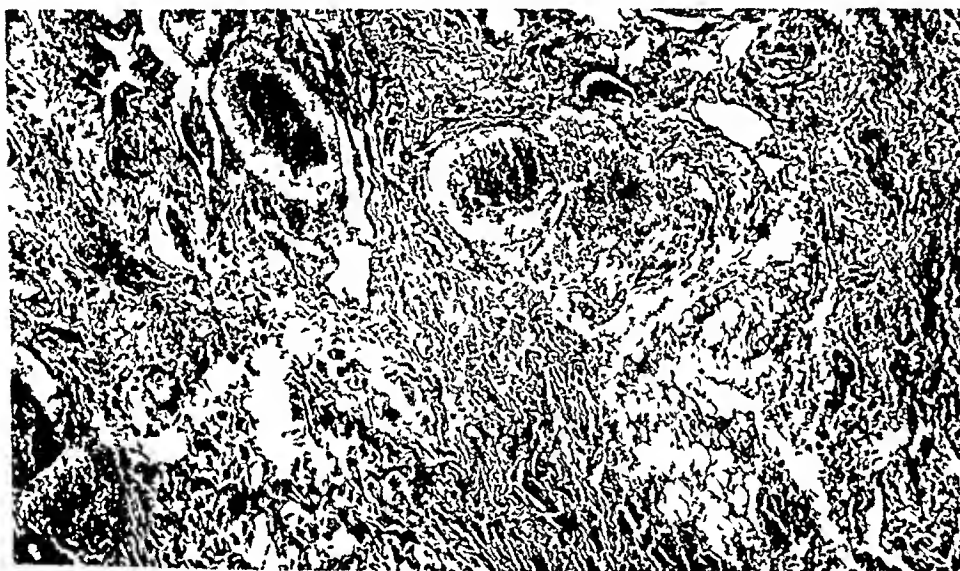


FIG. 3.—Showing cavernous and capillary hemangiomatous infiltration, with an area of fatty infiltration.

DISCUSSION

This case was deemed of interest since only three instances of glomus tumor in deep structures, away from the ends of the extremities, appear in the literature,^{7, 8, 9} and only one⁹ is this country. However, on review of the published reports of these cases there was considerable doubt in the author's mind as to the correctness of the diagnosis. Murray and Stout,¹⁰ in 1942, have identified the epithelioid cell of the glomus tumor as the pericyte of Zimmermann. Stout has investigated the *tuberculum dolorosa*^{5, 10, 11} extensively and is certainly an authority on them. The sections from this case were sent to Doctor Stout, who very kindly examined them, and expressed the opinion that this was a case of venous hemangioma¹² because the pericytes (if any) do not regularly surround all vessels. He also rejected the diagnosis of hemangiopericytoma, recently described by Stout and Murray.¹³

As noted above, hemangiomata are a rare cause of paroxysmal pain, such as occurred in this case, being found in only 0.01 per cent of 2081 cases⁷ (five per cent of 40 cases in which presence of pain was specified) of cutaneous and subcutaneous tubercles. Stout⁵ was unable to attribute the pain experienced in his cases to any one physical abnormality. The fact that our case continued to have pain for a period of two weeks after extirpation

of the tumor, is suggestive that, here, a nervous mechanism was the cause of pain and painful impressions continued to be transmitted during the healing period. This is apparently the fourteenth case of a typical *pes equinus* deformity due to hemangioma of the calf muscles¹⁰ and this lesion, although rare, should be taken into consideration in determining the cause of this deformity. A correct preoperative diagnosis has been made in only 18 per cent of reported cases of angioma of skeletal muscle. The presence of a palpable mass and roentgenologic evidence of phleboliths are the only objective manifestations of this lesion.

Since these lesions produce a great amount of disability, which is almost certainly relieved by excision, correct diagnosis and treatment is very important.

SUMMARY

1 A case of venous hemangioma of the gastrocnemius muscle is presented.

2 The "tip-toe" deformity exhibited by this patient has been reported in thirteen other identical cases.

3 The paroxysmal pain which is characteristic of glomus tumors and some leiomyomata may also occur in hemangiomata, and less frequently in other tumors.

4 Dramatic relief from marked disablement is possible by extirpation of these tumors.

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VENOGRAPHY*

I—ITS USE IN THE DIFFERENTIAL DIAGNOSIS OF THE PERIPHERAL VENOUS CIRCULATION

II—A SIMPLIFIED TECHNIC

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THE ELUCIDATION of many of the problems in the study of the venous return in legs which present varicosities, massive edema, and ulceration has been made by certain excellent clinical tests. The observations of Trendelenberg, Perthes, and Homans have done much to clarify these situations.

In spite of painstaking study, however, it is not possible, in all cases to determine the status of the venous circulation with certainty by clinical methods alone. In many cases several logical possibilities present themselves. It has been possible in our clinic to demonstrate the exact status of the venous return by venography.

J. C. Dos Santos¹ has described an excellent method for the roentgenologic study of the veins of the lower leg. This method was modified by Bauer,² and utilized by others,^{3, 4} for the study of postoperative deep venous thrombosis.

The technic is quite simple. The heel is elevated on a six-centimeter block and rests on its mesial surface. Under local anesthesia a two-centimeter incision is made about one centimeter behind the external malleolus. The lesser saphenous vein is isolated here. It drains into the deep venous system. The distal portion is tied with fine silk, and a small cannula is inserted into the proximal portion. Twenty cubic centimeters of a 35 per cent diatrizoate solution (Winthrop‡) is injected. The injection rate is uniform and takes about 60 seconds. The roentgenogram is taken during the injection of the last few cubic centimeters. By using a 14 x 17 film in its longest dimensions, and placing the lower end eight to ten centimeters above the ankle it is possible to visualize the deep venous circulation of the calf and a good portion of the femoral vein. The cannula is removed and the vein tied. The skin is closed with silk after lavage of the tissues with saline to remove any residual diatrizoate, which is quite irritating to the tissues.

We have found it possible, in most cases, to modify this technic by direct venopuncture into a superficial vein on the lateral side of the ankle. With a tourniquet around the ankle, a No. 21-22-gauge needle is inserted into the most prominent vein on the anterolateral surface of the ankle. The tourniquet is then released and the remainder of the procedure is completed as described. This obviates the necessity of incision in most

* Prize Essay, North End Clinic, Detroit, Michigan, July, 1942.

† Lieutenant, M.C., 39th Evacuation Hospital, Camp Atterbury, Indiana.

‡ Kindly supplied by the Winthrop Chemical Co. for this problem.

cases We have also found that better visualization of the deep venous tree is secured by an exaggerated Trendelenberg position The application of a tourniquet below the groin prevents loss of the dye before the picture is taken and causes more complete filling of the deep system This has

revealed complete filling of the calf veins in a case (Case 3) which appeared to show deep calf thrombosis by the usual technic We have had no reactions with the diadrast and no evidence of thrombosis following its use

The following cases present a few of the problems which we felt have been clarified by the use of venography

ILLUSTRATIVE CASE REPORTS

Case 1—D K is a patient with varicose veins but no leg swelling or clinical evidence of impairment of the deep venous circulation A venogram was taken by employing the usual technic to demonstrate the intact deep venous system This shows complete filling of the venous tree (Fig 1)

Case 2—J F is a 50-year-old male with a chief complaint of painful left leg The patient had had varicose veins for at least 12 years These were treated by ligation, with a series of circular incisions in the middle and upper right leg and lower thigh in 1931 The legs continued to swell and became worse after a series of six injections They became very painful Examination reveals reddish-brown induration in lower half of right leg and ankle Prominent varicose veins present

FIG 1—A normal deep venous tree in a patient with varicose veins (A) Popliteal vein (B) Anterior tibial vein (C) Posterior tibial vein

on medial aspect of lower thigh extending to calf Questionable positive Trendelenberg test obtained in right leg During the course of treatment Unna boots were applied The patient had recurrent attacks of superficial phlebitis Ace bandages made the extremities more painful

A venogram was made which showed only a short segment of the deep system communicating with a large dilated superficial varicose vein carrying the entire venous return of the extremity (Fig 2)

COMMENT This case presented a problem in diagnosis because of the presence of a large varicose vein which was thought to play a rôle in this patient's symptomatology It was even suggested that ligation of this vessel should be done before the picture was seen The roentgenogram

however, showed, quite convincingly, a condition which necessitated the complete function of these "compensatory superficial varicosities." All occlusive methods of therapy were then abandoned with moderate relief of symptoms.

Case 3—F D This 18-year-old girl noticed left calf hypertrophy for one year. No other complaints. Past history was noncontributory. No history of trauma, phlebitis, or diphtheria. Examination reveals marked enlargement of the entire left

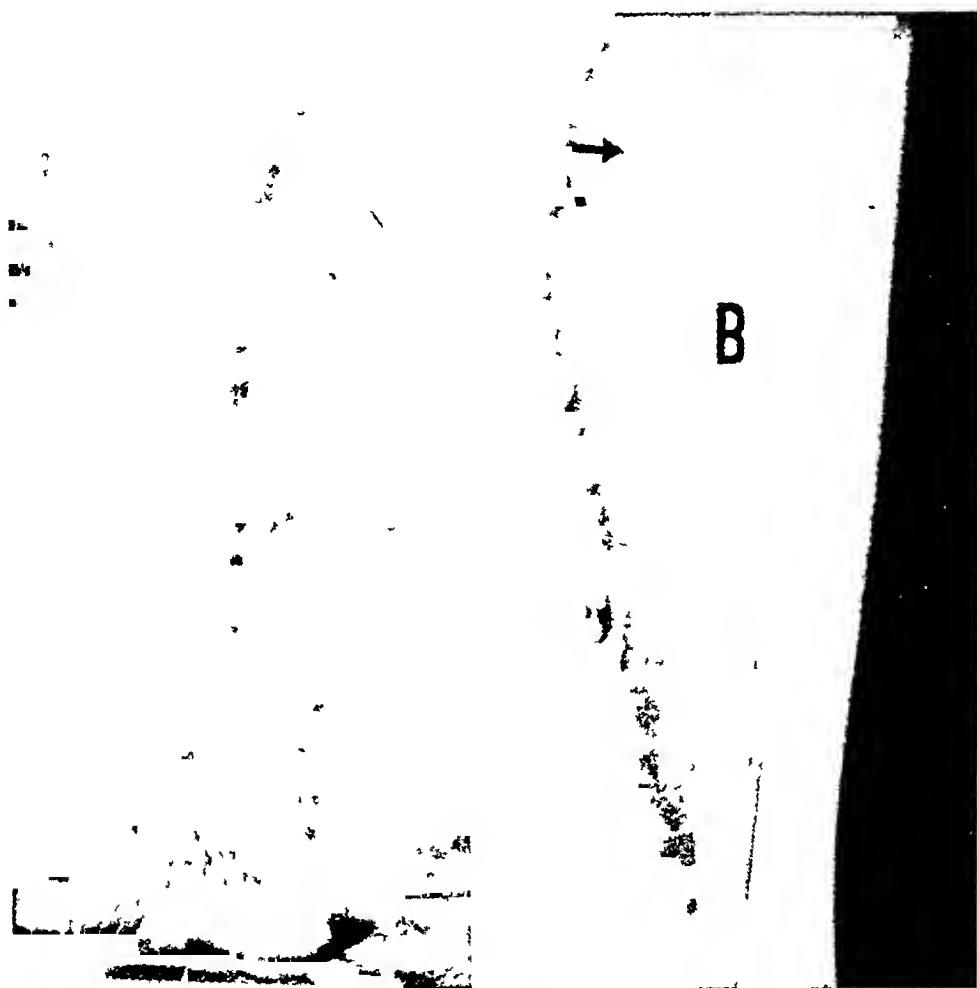


FIG 2—Obstruction of the deep venous system with compensatory varicosities (A) Large superficial varicosity, the only venous return from the leg (B) Communicator to the small remaining segment of posterior tibial vein

leg with pronounced calf hypertrophy and varicosities. No tap impulse in the thigh. Questionable fibrous mass in the calf. A roentgenogram of the leg showed thickening of the soft tissues. A venogram showed complete absence of the deep venous system and numerous prominent superficial vessels ending in teat-like projections. A venogram was made of the opposite leg to rule out any bilateral congenital venous abnormality. This was normal. A diagnosis of deep thrombosis with compensatory varicosities was made. A biopsy was advised to rule out angioma.

COMMENT Several months later another check-up venogram was done on this leg because of the several suspicious teat-like projections of the superficial vessels. At this time a tourniquet was applied below the groin and a picture taken in Trendelenberg position. This roentgenogram revealed complete filling of the deep venous system. There were several marble-

size venous outpocketings in the deep vessels above the knee with numerous intercommunications, a picture which we have not seen before. Exploration was suggested but has not been done (Fig 3)

Case 4—A W, a 48-year-old female, had a "milk leg" 16 years ago. This was followed by varicosities. A high saphenous ligation was performed, with relief of discomfort. There was then a recurrent right internal saphenous vein from the midthigh and many new varicosities in the lower right leg associated with marked edema. A midthigh ligation was done, with retrograde injection of sodium morrhuate. This was immediately followed by marked leg edema and pain. The status of the deep circulation then came up for discussion, since swelling and leg pain followed so promptly after superficial venous obliteration. An attempt was made to obtain a venogram by the incision technic of Bauer, but all the vessels were scarred, and no bleeding was obtained. A superficial lateral ankle vein was then injected by direct venopuncture and an excellent venogram obtained. This showed a perfectly normal intact deep venous system.

COMMENT This patient had massive lymphedema. In this case, contrary to Case 2, we advised continuation of iontophoresis and supportive Ace bandage with moderate relief.

Case 5—H L, a 52-year-old man with a complaint of left leg pain on arising and heavy feeling in the leg. History of a deep penetrating injury of lower right thigh followed by swelling for some time. Recent Bell's palsy. *Examination* reveals chronic edema of both legs, with desquamating pigmentation and varicose veins of the left calf. Normal arterial pulsations. Ace bandages were advised for the varicose veins. The patient could not wear these because of increased calf pain. This suggested the possibility of deep venous occlusion. A venogram showed a normal deep venous system and moderate arteriosclerosis.

COMMENT Apparently, our varicose vein picture plus arteriosclerosis was justified. Pain after the Ace bandage was not due to deep venous block but probably to ischemia on the arterial side. Obliteration of the superficial varicosities was justified. In a case of this kind complicated by several factors, it certainly would be injudicious to obliterate the varices without absolute knowledge of the status of the deep venous system.

Case 6—G H, a 67-year-old man complained of rheumatism of the right hip. History of a gunshot wound of the right antecubital fossa, with operative repair 25 years ago. He now has a local tumor, dizziness and tinnitus. *Examination* reveals an arteriovenous aneurysm over anterior portion of right antecubital fossa with moderate enlargement of the arm. B P 174/0 right arm, 174/104 left arm. Moderate cardiac hypertrophy. An arteriogram was taken by direct injection of 20 cc of diodrast into the brachial artery proximal to the aneurysm. This showed multiple arteriovenous communications over an area, four by six centimeters in length in the antecubital space.

COMMENT This case showed hypertension and cardiac hypertrophy following an arteriovenous aneurysm. Resection was decided against because of the age of the patient. With the arteriogram it is possible to visualize

the extent number and location of the arteriovenous communications in case operative procedure is feasible

Case 7—M L, a 44-year-old white male, with recurrent migrating phlebitis for more than 12 years. The patient had had a saphenous vein ligation. For two or three months there was persistent pain and coldness of the right foot and marked intermittent claudication. Examination reveals a cold, blue right foot, with painful toes. Absent dorsalis pedis and posterior tibial pulsations. Dilatation of the calf veins and positive tap test in the thigh. Negative Perthes'. A diagnosis of Buerger's disease and varicose veins was made. The deep system was thought to be intact. A venogram was done



FIG 3—Venogram of a case with left calf hypertrophy. (A) Deep venous system. (B) Bulbous dilatation of vein. (C) Multiple intercommunications with bulbous venous dilatation.

to visualize the venous changes in Buerger's disease. This showed widely dilated posterior tibial and deep femoral veins with marked irregularity of intima. There were filling defects of the lumen where thrombi were adherent.

COMMENT This is the only picture we have seen of the marked changes taking place in the deep venous tree in a patient with obvious Buerger's disease (Fig 4).

Case 8—P C, a 55-year-old female, with extensive varicose veins for many years, most extensive in the right leg. There was a prominent right long internal saphenous vein. These were not controlled by a tourniquet at the saphenofemoral junction and a tourniquet applied to large veins above and below the knee.

COMMENT A venogram demonstrated four communicating branches from the superficial varicosities of the calf to the deep system. Clinically, these are incompetent. Therefore, the only cure for this patient is a flap

operation to secure each perforator. A high vein ligation and a division of one low branch would result in failure (Fig 5)

Case 9—K. C., a 58-year-old white man, developed a postoperative phlebitis following prostatectomy eight months ago. The patient remained in bed for six weeks, with marked swelling of the leg. He could walk for only five minutes before treatment. He was improved greatly with Ace bandage and iontophoresis.



FIG. 4.—Venogram of a patient with Buerger's disease. (A) Femoral vein with multiple filling defects, the site of thrombi. (B) "Splintering" of intima in posterior tibial vein with thrombi.

COMMENT A venogram showed many collateral superficial vessels and absence of the deep venous system of the calf. This picture is characteristic of the great majority of postoperative phlebitis in the location of the venous obstruction (Fig 6 and Discussion).

We have studied a number of additional cases by venography in which there was real doubt as to the nature of the deep venous system. In these

cases venography demonstrated that the deep venous channels were intact and it was possible to proceed with definitive therapy to cure the symptoms and disability caused by the varicosities present

DISCUSSION—The common postoperative and postpartum disorders of venous thrombosis were thought to be due to deep femoral or peripelvic thromboses. Homans,⁷ in 1937 pointed out that the popliteal region and upper calf were probably frequent sites of thrombophlebitis. Roessle,⁶ in 1937, found deep calf vein thromboses in 88 of 324 autopsy cases where



FIG. 5.—Extensive varicose veins with multiple incompetent communicators clinically (A B C D). All point to perforating branches between superficial and deep venous systems.

thorough dissections were done. Thirty-eight had, in addition, thromboses in the femoral vein. Ten had massive pulmonary emboli arising from the femoral vein, but, in addition, there was thrombosis of the calf vein in these cases. Neuman,⁷ 1938, has similar figures from postmortem material. Calf thrombosis occurred in 73 per cent and calf thrombosis with femoral thrombosis in 16 per cent. Most conspicuously, however, *there is no case of femoral vein thrombosis with unaffected calves*. Frykholm,⁸ in 1939, with careful dissection of 133 cases of venous thrombosis, found 85 per cent occurring distal to the profunda in the femoral vein and primarily in the branches below the knee. Bauer,² in 1940, has confirmed this data in the living subject by venography. He has an excellent study of venograms taken to diagnose early postoperative calf thromboses and older healed processes.

In our clinic, an attempt has been made to clarify many of the obscure cases of chronic leg swelling and leg pain in which the status of the venous and lymphatic circulation cannot readily be determined by the usual clinical tests. It was possible to demonstrate a normal deep venous return in the calf of the great majority of chronic leg swellings with or without pain. Chronic lymphedema was thought to play a dominant rôle in the pathogenesis of this condition. It is possible that chronic sepsis may play an important rôle in these cases. This idea was first suggested by Halsted⁹ to explain chronic swelling of the arm following radical mastectomy. The use of chemo-

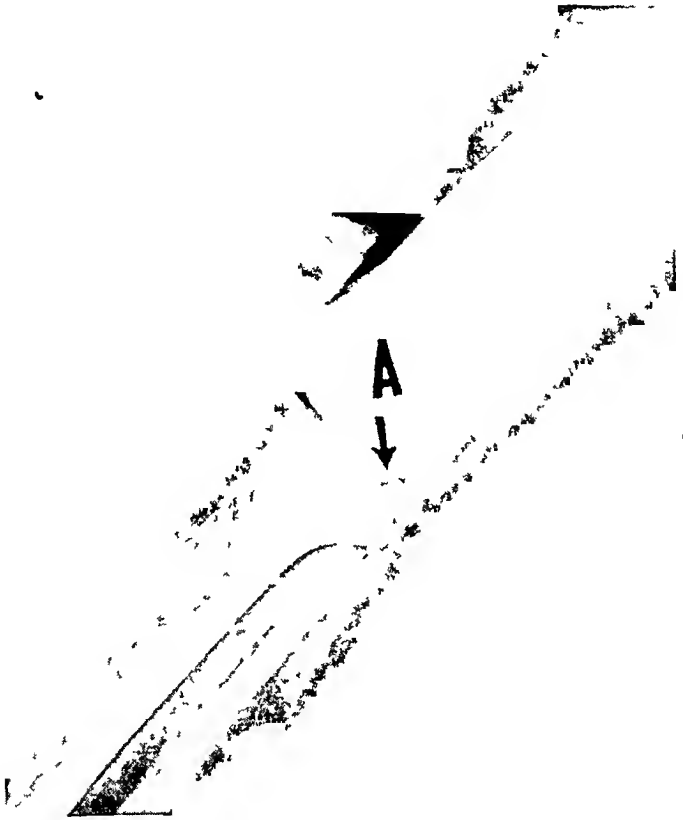


FIG. 6—Postoperative deep calf thrombosis. (A) Shows the termination of the popliteal vein. No deep venous system is visualized in the calf.

therapeutic drugs of the sulphonamide series may be helpful to stop the inflammatory process. We are treating some of these cases of chronic leg swelling and pain without venous obstruction with these drugs. The results will be described in a later report.

It is necessary to be absolutely assured of the deep circulation in those cases of leg swelling and pain with marked varicosities where the treatment of choice involves sclerosis of the varicosities and high saphenous vein ligation. Case 2 is such an instance, where obliteration of the compensatory varicosities would remove the only remaining venous return in the leg.

It is also possible by the use of this technic to study those not infrequent cases of unilateral calf hypertrophy for circulatory disturbances as in Case 3.

In arteriovenous aneurysms, where surgery is contemplated, it is of more than academic interest to visualize the extent and situation of the arteriovenous anastomoses, a visualization which is not always simple or safe at the time of operation. It is possible to determine the number of communications, since in some cases multiple openings are present.

CONCLUSIONS

- (1) A simplified technic for venography is described.
- (2) Its utilization in a number of perplexing cases of leg swelling and pain with or without varicosities has been described.
- (3) An interesting roentgenogram of the deep venous tree in Buerger's disease is shown.

Appreciation is extended to Dr S Rosenczweig, Dr A Bloom, and the other members of the Cardiovascular Clinic of the North End Clinic for their helpful cooperation.

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A SUBCLAVIAN ANEURYSM CURED BY CELLOPHANE FIBROSIS

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THREE YEARS AGO, Pearse¹ reported to the American Surgical Association that he had been successful in producing a gradual occlusion of the aorta in dogs. Wrapping the vessel with ordinary DuPont cellophane had led to a fibrosis which had eventually closed it off by its contraction. The ability of cellophane to produce this type of tissue reaction was used by Page² in the production of perinephritis with persistent hypertension. We ourselves have had occasion to study this fibrosis in experimental work on herniae.

Since the above report was made, we have had the opportunity to try out the method in two human cases. One of these attempts was successful, as indicated by the title of this paper, while the other eventuated in ligation of the involved artery with an unsatisfactory result.

Case 1—On July 7, 1941, Hussein bin Mohammed, a weather-beaten, old pearl diver, age 70, or more, reported to the Mason Memorial Hospital complaining of very severe pain in his left shoulder. It was not entirely clear just when this pain started but apparently it had excited his attention for less than six months. Its intensity had greatly increased during the few preceding weeks.

Physical Examination—The patient was a thin, hardy old man, in good general condition. The pain which was distressing him arose from a pulsating mass the size of a hickory nut, which appeared to be connected with the third portion of the left subclavian artery. There was a loud bruit and usually a palpable thrill. The pain radiated up into the neck and to some degree to the shoulder and upper arm. The mass itself was not tender. The systolic blood pressure in the left arm varied, but a reading of 130/70 was usually obtained. Roentgenologic examination of the shoulder area was negative. The Kahn test was negative. **Clinical Diagnosis** Aneurysm of the third portion of the subclavian artery. Although it was realized that ligation of the subclavian can usually be carried out without gangrene of the extremity, it was decided to try the effect of cellophane fibrosis on this case.

Operation—July 8, 1941. Under local anesthesia, with one per cent novocain solution with adrenalin, the mass was exposed by a three-inch incision below the clavicle. The intervening muscles were cut in the line of the incision. Adequate exposure was easily obtained. The aneurysm presented itself as a fusiform swelling in the course of the artery, about 2.5 cm in length and 1.5 cm in diameter. Two small arteries coming off the dilated portion were doubly ligated and cut. The aneurysm was carefully exposed and slightly more than one centimeter of normal artery both proximally and distally (Fig. 1).

Cellophane tape, one centimeter in width, was boiled and ready for use. We found that boiling is not the best way to sterilize the tape, because it was rendered so bodiless and fragile that it was almost impossible to lay it in place accurately. A five-layer band was applied proximally, and fastened with a single suture on the anterior surface. A less satisfactory application was made distally, after which the muscles were brought together as accurately as possible, and the skin was sutured.

The operative wound healed without incident. He developed an attack of malaria

in the hospital which was treated with quinine. His pain was unrelieved by operation. He had been told in advance that this would be the case, but he was much disappointed. He was discharged on the seventeenth postoperative day, after he had promised to return for inspection every month.

Subsequent Course—In spite of his promise, the patient did not return for follow-up visits. In May of the next year, we posted a reward of five rupees for his discovery, and found him living only five miles away. He was now delighted with the result of the operation, for the pain was almost gone and he was planning to return to his work as a pearl diver. For our part, we were much disappointed, for the aneurysm was no smaller. Indeed it seemed definitely larger, although this may have been due to atrophy of the overlying muscles which brought it closer to the examining finger. Moreover, its pulsatile thrust seemed as strong as ever. Between the aneurysm and the entering artery was a sharp groove which, at this point, reduced the diameter of the artery by at least one-half. This groove was astonishingly narrow, and we wondered if it would have been better to use a wider tape (Fig. 1 C).

The patient's general condition was good. He had improved somewhat with the disappearance of the pain. We hoped, but by no means felt sure, that there would be no further enlargement of the aneurysm. In any case, the fibrosis has progressed encouragingly. It seemed that with a little further contraction, the aneurysm must begin to shrink in size.

On October 28, 1942, five months later, the patient was observed again. He had not returned to his pearl diving because of age and general pains, but apparently it was not the aneurysm that kept him home. We were delighted to find that the aneurysm had shrunk until its diameter was about the same as that of the artery. The examining finger following the subclavian artery now felt only two sharp grooves, separated by one and one-half centimeters. It was interesting to note that the pulsatile thrust of this small remnant of the aneurysm was not notably less than that of the artery proximal to it. The systolic blood pressure was more stable now. It was maintained on the left side at a level about ten points higher than that on the right (left, 130/70, right, 120/80).

On February 8, 1943, the patient was looked up again. It was expected that the aneurysmal sac would be completely obliterated by this time, and this hope was not disappointed. The subclavian artery was interrupted by a deep groove, filled with a fibrous mass (Fig. 1 E). The size of the mass was difficult to determine, it was perhaps slightly more than half a centimeter in length. The pulse on the left side was perceptibly delayed as compared with the right. The blood pressure on the left was 136/96 on the right 120/72. There was no pain in the shoulder area, and cure appeared to be complete.

Case 2—Jebber Musellim, a pearl broker, age about 70, came to the Mason Memorial Hospital, March 22, 1942, complaining of severe pain in the left shoulder. The history was very similar to that of the first case. The pain had increased so much during the preceding 48 hours that he was rather desperate and insisted that something be done at once.

Physical Examination—The patient, a tall, thin man, in good general condition, except for the presence of bronchitis. Below the lateral portion of the left clavicle was a pulsatile mass, apparently a little smaller than that in Case 1. There was a loud bruit and palpable thrill.

The patient's pain was so severe that we urged him to come in at once for treatment. We explained that we greatly feared rupture and would suggest immediate operation. The patient refused this, and decided to try Arab medicine, and, sick as he was, he went home, where the region of his pain was branded with a red hot iron in a number of places. One vertical brand half an inch wide and nearly two inches long,

was placed exactly over the pulsating swelling. These brands relieved the pain a little and he remained away from us for 48 hours. At the end of this time, he appeared and begged for the operation. He had been given sulfapyridine tablets to use at home, and his bronchitis was better. However, his temperature ranged from 100° to 101° F. The systolic blood pressure in both arms was 136. The Kahn reaction was negative.

Operation—March 24, 1942. The exposure of the aneurysm was similar to that of Case 1. However, the skin incision was complicated by the presence of the branded areas. These areas had been cleaned with great care, and touched with carbolic acid. The incision missed all of them except the vertical brand over the swelling itself. In spite of these procedures, wound infection, which almost cost the patient his life, ensued. The futility of trying to sterilize the necrotic skin was obvious.

The aneurysm was found to be about 15 cm in diameter. Distally, two branches of equal size left the swelling. Cellophane tape was wrapped about the artery proximal to the enlargement, and around each of the large distal branches. This time, the cellophane had been sterilized by a two-day immersion in alcohol instead of boiling and it was easily handled.

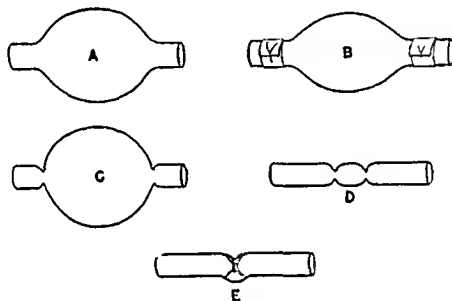


FIG. 1.—Diagrammatic representation of changes in aneurysm in Case 1. A. Pre operative impression. B. Immediately post operative cellophane applied. C. Condition at time of first follow up examination May 1942. D. Marked shrinkage of aneurysm noted Oct. 28 1942. E. Last observation Feb. 8, 1943.

On the fourth postoperative day it was realized that infection had set in. On the sixth day the incision was reopened, with the escape of an ounce of pus. The infection seemed to be clearing up until, at midnight on the eleventh day there was a profuse hemorrhage from the wound. The patient was found in a pool of blood, the bleeding having stopped for the moment. He was taken to the operating room and the wound was explored. There was found a tear of one of the ligated distal branches. The opening was plugged by a friable clot, which came away when touched, causing alarming hemorrhage again. This was checked by lifting the artery by means of its cellophane collar and temporarily occluding the lumen. It was out of the question to deal with this situation by means of cellophane tapes, so a triple ligation was carried out. The wound was then closed about a small drain.

The patient was given saline and glucose infusions. His left arm was kept encased in cotton wool. For the first 24 hours the arm was cold, and the patient complained of great pain. Following this it gradually became warmer, and within a week the pain had practically disappeared. There was no definite paralysis but rather a general weakness of all muscle groups. The patient remained in the hospital 31 days. His wound healed firmly. There was no further hemorrhage. The weakness of the left arm did not improve and wasting of the arm became increasingly evident. At the time of his discharge, the circumference of the left arm at the midbiceps level

was three centimeters less than the right. There was marked interosseous atrophy. Small objects, such as a pen, could not be picked up.

About four months after the operation, a Pavaex machine was secured, and a half-hour of treatment was applied every other day for three months. There was slight improvement so that he can now handle small objects better. It is probable that the arm will be permanently crippled.

SUMMARY

1. An aneurysm of the distal portion of the subclavian artery has been cured by means of the fibrosis induced by cellophane tape wrapped around the vessel.

2. It took ten months for the arterial occlusion to progress sufficiently to cause the aneurysm to diminish in size and 19 months for the process to be completed.

3. A comparable case was treated by ligation, with the result that there is considerable disability in the arm.

4. We believe that this method of gradual arterial occlusion is valuable, and that it might be applied to aneurysms of other arteries notably the aorta.

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THE COAGULABILITY OF VENOUS BLOOD OF NORMAL AND DISEASED LEGS*

A STUDY ON 191 SUBJECTS

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THERE has been in recent years a gradually increasing interest in the differences between the blood of diseased and that of normal extremities. Thus, blood drawn from varicose veins associated with complications has been found, on the basis of comparison with values accepted as normal, to exhibit an increase in viscosity and in the concentration of plasma proteins,¹ in carbon dioxide combining power,² and in the rate of sedimentation.³

The clotting time, also, has been studied, and while in the venous blood of thrombo-angitis obliterans, it was found by Theis⁴ to be shortened in some cases even to less than one minute, in the blood drawn from varicose veins, it was found to be "within normal limits." However, the normal values for viscosity, concentration of plasma proteins, of the carbon dioxide combining power, and of the rate of sedimentation, do not vary within the wide range that the clotting time does, so that a clotting time could vary 300 per cent and still remain "within normal limits." In order, therefore, to determine if there are any actual changes in the clotting time of the local venous blood of an extremity, it would be more reliable to use not the figures accepted as within normal limits, but the clotting time of the blood drawn at the same time from the normal extremity of the same individual. In the following study, this criterion was observed, the venous blood of a normal upper extremity serving as a control.

METHOD—One hundred ninety-one subjects, comprising four principal groups, were studied. Group I consisted of 28 normal students who had no detectable peripheral vascular disease. The results from this group serve as control for the evaluation of results obtained in the subsequent groups. Group II consisted of 115 patients with varicosities of the lower extremities which were being treated by injections of sodium morrhuate. In this group were many advanced cases with such complications as varicose ulcers, dermatitis, or peripheral edema of the affected extremity. Determinations of the coagulation time of the blood in the latter individuals, who had been treated with sodium morrhuate, were made only after one to three weeks had passed since the last treatment. In Group III there were 36

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COAGULABILITY OF VENOUS BLOOD

subjects suffering from conditions comparable to those in Group II, excepting that these patients had never received any treatment. Group IV comprised seven cases of postoperative venous thrombosis and five cases of primary acute thrombophlebitis.

The coagulation time of the blood from the upper and lower extremity was determined in each individual. Blood from the upper extremity was obtained from a cubital vein, that from the lower extremity from the internal saphenous vein at the ankle when there was no varicosity, as in Groups I and IV. In cases in whom there were varicose veins, as in Groups II and III, the blood was drawn from a varicose vein which had not been previously injected.

The determination of the clotting time was carried out according to the technic of Lee and White.⁷ The vein was pierced by a fine hypodermic needle after the application of a tourniquet, and one cubic centimeter of blood was drawn rapidly into a dry syringe. One-half cubic centimeter of blood was placed each in one of two small test tubes and duplicate determinations made simultaneously by two observers. The test tube was tilted at regular intervals until it could be inverted without displacement of the blood mass. This was taken as the critical point for the clotting time. The test was repeated when delay or difficulty was encountered in the process of withdrawing blood from the vein or when any other fault in technic occurred. In 191 subjects 352 duplicate sets of determinations were made. In none of these was there a difference greater than 20 seconds in the determinations of the two observers, most of the differences being in the neighborhood of ten seconds. The values of the clotting time of the blood from the arm and leg were compared, and the results tabulated in Tables I and II.

TABLE I
ANALYSIS OF INCREASED COAGULABILITY OF BLOOD OF LEG

Group	Total No. of Cases	No. of Cases with Hypercoagulability	Per Cent of Total	Acceleration in Excess of 59 Seconds		Average Acceleration Time	Maximum Acceleration Time
				No. of Cases	Per Cent of Total		
I	28	17	60%	0	0%	30"	59"
II	115	83	72%	39	33%	70"	285"
III	36	28	77%	13	36%	60"	132"
IV	12	11	92%	9	75%	146"	284"

RESULTS.—Referring to Table I, one observes (1) That there is a slight tendency for venous blood from the lower extremity of normal individuals (Group I) to clot more rapidly than that from the upper extremity, i.e. in 60 per cent of the total number of cases. (2) The blood from varicose veins of individuals in Groups II and III showed an exaggeration of this tendency to faster clotting (72 and 77 per cent, respectively) than the venous blood from the upper extremities of the same individual. (3) In the cases with thrombophlebitis (Group IV) blood from the lower extremity clotted more rapidly than that from the upper extremity in 92 per cent of the cases. (4) Taking those cases of all Groups in which the blood

clotted more rapidly from the lower extremity the average acceleration in Group I was only 30 , whereas in Groups II and III comprising the varicose veins, the average acceleration was 70 and 60', respectively, and in those cases of Group IV with thrombophlebitis the average acceleration was 146". The greatest acceleration in Group I was in one individual, and that was 59'. In Group II, the maximum acceleration was 285', while in Group III it was 132. Thirty-three and 36 per cent of the cases with hypercoagulability of varicose vein blood for the two respective groups showed acceleration times in excess of the 59 , noted above as the maximum for normal individuals. In Group IV, the maximum acceleration time was 284", while 75 per cent showed acceleration times in excess of 59'.

It was previously stated that there was a difference of about 10 to 20 seconds in the determinations by the two observers on any one blood. This may be considered as inherent in the technic. Making allowances in one case for an experimental error of ten seconds and in another case of 20 seconds, the results may be regrouped as in Table I which may be analyzed as follows:

TABLE II

ANALYSIS OF COMPARATIVE COAGULABILITIES OF VENOUS BLOOD OF UPPER AND LOWER EXTREMITIES-REGROUPED ON BASIS OF OBSERVATIONAL ERROR

(A) 10 Second Observational Error

	Group I	Group II	Group III	Group IV
Equal	5 (18%)	18 (16%)	9 (25%)	0 (0%)
Leg > arm	15 (53%)	80 (69%)	24 (64%)	11 (92%)
Arm > leg	8 (30%)	17 (15%)	3 (9%)	1 (8%)

(B) 20 Second Observational Error

	Group I	Group II	Group III	Group IV
Equal	13 (46%)	35 (30%)	12 (33%)	0 (0%)
Leg > arm	12 (43%)	72 (62%)	23 (64%)	11 (92%)
Arm > leg	3 (11%)	8 (8%)	1 (3%)	1 (8%)

For the normal individuals in Group I in the 10-second range of error, only 53 per cent of the cases showed hypercoagulability of lower extremity blood as compared with the upper extremity blood while the clotting time of the upper extremity blood was faster in 30 per cent of the cases, the remaining 18 per cent being equal. In the 20-second range of error tabulation, blood from the lower extremity clotted more quickly in only 43 per cent of the cases, while upper and lower extremity blood coagulability was equal in 46 per cent of the cases. In no instance did the blood of the lower limb clot more rapidly than the blood of the upper limb by more than 59".

In Groups II and III, however, the results were definitely different. In the ten second range of error tabulation, the blood from the varicose vein was hypercoagulable as compared with the venous blood of the upper extremity in 69 per cent of the total cases in Group II and 64 per cent of the total cases in Group III. The upper extremity blood was more coagulable in only 15 and 9 per cent of the cases for the two respective groups. When the range of error was set at 20 , the same tendency is to be observed. Sixty-two of the cases in Group II, and 64 per cent of those

in Group III, showed a greater clotting tendency of blood from the varicose veins, whereas in only eight and three per cent, respectively, did the venous blood from the upper extremity clot more rapidly. In Group IV, 92 per cent of the total cases showed the blood from the lower extremity to be more coagulable than upper limb blood, whereas the reverse was true in only eight per cent of the cases, these results being the same whether the range of error was as 10 or 20.

In those cases where thrombophlebitis had already become established, there was also an associated marked change in the coagulability of the blood of the diseased extremity as compared with that from a normal extremity of a thrombophlebitis individual. This is plainly visible in the tables. In Groups II and III, it is likewise seen that there is a strong tendency for the same to be true, although not with as great a frequency. This is probably due to the great variation of the degree of disease in the affected vein in both these groups, whereas in cases with established thrombophlebitis the maximum degree of disease of the affected vessel had taken place. In other words, there are a number of cases in both Groups II and III in which the disease of the affected vessel was so mild as not to interfere with the characteristics of the blood therein. These cases detract from the percentage which might be high enough to present significant differences in the characteristics of blood in a vessel with well-established disease.

There is, thus, a distinct tendency towards acceleration of coagulation in the blood of varicose veins. Where such differences occurred, the magnitude was two times greater than the average difference of the normal individuals, and the maximum difference was five times greater than the maximum difference of the normals. In the cases with established thrombophlebitis this hypercoagulable tendency of blood of the diseased extremity was so marked, that the average acceleration was four and one-half times greater than in normal subjects, and the maximum five times greater.

COMMENTS—Some speculations evoked by the above findings may be set down in an attempt to relate this work to its possible clinical use. In regard to the subject of varicose veins, the following questions arise: (1) What change takes place in the blood of a diseased extremity which is reflected in the increased tendency of the local blood to clot more readily than that from the normal extremity of the same individual? (2) Does this rapidity of clotting increase with the functional impairment of the physiology of the veins? (3) Does it disappear in the recumbent position? (4) Do varicose veins showing this hypercoagulable tendency predispose to the development of postoperative thrombo-embolization?

In regard to the marked acceleration of clotting of blood from the veins of extremities with established thrombophlebitis another set of questions may be set down: (1) Is this tendency due to the same change as is to be found in varicose vein blood? (2) Does it antedate the formation of the thrombus?

(3) If so, may it not be developed into a prognostic test which would indicate preventive therapy before actual thrombo-embolization takes place? Each of the answers to these seven questions would constitute the definitive result of seven lines of further investigation

SUMMARY

1 A study of the coagulation time was made of the blood from the upper and lower extremities of 191 subjects—28 normal, 156 with varicose veins, and seven with established thrombophlebitis

2 There was found in normal persons, a slight tendency of lower extremity blood to clot faster than upper extremity blood

3 This tendency was moderately exaggerated, in various degrees, by the presence of varicose veins and markedly exaggerated in the blood from thrombophlebitic extremities

4 The possible implications of these findings were discussed

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BOOK REVIEWS

THE HEMORRHAGIC DISEASES AND THE PHYSIOLOGY OF HEMOSTASIS By A J Quick, M D Charles C Thomas, 340 pp, \$5 00, Springfield, Ill, 1942

This work, which is an expansion of the Beaumont Lectures given by the author in 1941, represents the first methodical and comprehensive effort to analyse the Hemorrhagic Diseases from the pathophysiologic standpoint. The author wisely stresses the fact that the work is not a treatise on blood coagulation. It intends to deal with this topic as one of the factors sharing in the mechanism of hemostasis. Alterations of this mechanism are regarded as the fundamental causes to be sought in the study of the Hemorrhagic Diseases.

Contradictory departures from his avowed purpose are, however, evident here and there. At the outset, a chapter deals not with the history of hemorrhagic disease or of hemostasis in general, but with the "History of the Coagulation Mechanism". Hemostatic factors other than those related to blood coagulation, e.g., vascular and extravascular factors, receive scant attention. For example, purpuras of the Henoch and Schoenlein type, which might well result from alterations in those factors, are dismissed with the remark (p 132) that "only the thrombocytopenic purpuras are primarily hemorrhagic diseases". Due prominence is given to the role played by the blood platelets in hemostasis. There is a good discussion of thrombopenia, its manifestations, course and treatment. Hereditary thrombasthenia (Glanzmann), the only authentic disorder of hemostasis due to a qualitative defect in the blood platelets, receives passing mention only. The reader is given the impression that this disorder should actually be grouped with the "pseudo-hemophilia" of von Willebrand, the cause of which resides probably in the vessels. Much confusion, however, exists even in the current medical literature, concerning these two diseases.

The author is at his best in the chapters dealing with blood coagulation. There he examines and reports fully, and, on the whole, impartially, the mass of evidence accumulated on this controversial subject during the past 50 years. The discussion is enlivened by the author's personal comment made pointed by intimate knowledge of a field in which he played such a leading part.

An appendix dealing with technical methods supplies directions for the performance of many tests, important information, unobtainable elsewhere, under one cover. The book should prove of great value to other workers in the field of hemostasis and its disorders. Throughout the text the reader may pick up stimulating leads, valid (even when tart) criticisms on method and interpretation and much imaginative spanning of seemingly unrelated facts. This reviewer knows of no similar work on the subject to date, in which the facts are so clearly exposed, the evidence so well grouped and shrewdly examined and its possible implications so brilliantly outlined.

LEANDRO M TOCANTINS, M D



ABDOMINAL AND GENITO-URINARY INJURIES, MILITARY SURGICAL MANUALS III, NATIONAL RESEARCH COUNCIL W B Saunders Co, 243 pp, \$3 00, Philadelphia and London, 1942

The soundness of the views expressed in this volume is attested by the membership of the Committee on Surgery of the Division of Medical Sciences of the National Research Council and its subcommittee on Urology, as well as by the experience and knowledge of Dr Ambrose H Storck, who prepared the section on Abdominal In-

juries, and of Dr Clark M Johnson and Dr H M Weyrauch, who contributed to the section on Genito-Urinary Injuries

It is so thoroughly sound and fair that it may not always help the isolated medical officer to a definite decision on the procedure he should follow

Certain procedures are definitely condemned and perhaps the book is most valuable for these warnings

WALTER ESTELL LEE, M D



FIRST AID, SURGICAL AND MEDICAL By Warren H Cole, M D, and Charles B Pucstow, M D, M S, Ph D Appleton-Century Co, New York 1942

The authors have compiled, with the assistance of a formidable list of contributing authors, a modern version of emergency treatment

The book is well arranged, beginning with the limitations and precautions of first aid work, proceeding with an intelligent outline of anatomy and physiology as a basis for the reader to appreciate the reasoning upon which subsequent chapters are based. The illustrations are good and the individual chapters on specific subjects are well arranged. The early use of the sulfa drugs is stressed, and there is an agreeable absence of antiseptic measures often noted in other texts on this subject.

An excellent chapter on transportation of the injured is included.

The problems of respiratory emergencies are treated as a group so that the student is prepared for the treatment of such emergencies occurring from either respiratory arrest or respiratory obstruction.

Medical emergencies in contradistinction to surgical emergencies are discussed, giving the reader an intelligent approach in caring for such conditions.

The book may safely be recommended as a guide for medical students as well as an advanced text for those who have had previous first aid training.

WILLIAM V HENLEY, M D

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MANAGEMENT OF ULCERS AMONG NAVAL PERSONNEL[†]

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AND

LIEUTENANT HUGH R BUTT, M C , U S N R †

GASTRO-INTESTINAL DISEASE constitutes a major problem among military personnel. Of more than 3,564 patients with dyspepsia, admitted to military hospitals in Great Britain, 55 per cent were found to have peptic ulcer. These figures include some reported from Naval hospitals. In the United States Army, in 1940, diseases of the digestive system ranked third as a cause for admission to sick report, fourth as a cause of death, and fifth as a cause of discharge for disability.⁷ Of all medical patients admitted to a general hospital of the United States Army, 18 per cent had symptoms of digestive disease.¹⁰

In spite of the statistics from Great Britain (Table I) and this country, there is little evidence to suggest an increase in peptic ulcer as a result of the present war but, as has been pointed out,² the war certainly has revealed the unexpected frequency of peptic ulcer in the civilian population before the war began. Several authors^{4, 6} have found that about 90 per cent of the soldiers with peptic ulcer in the Army of the United States had had ulcer prior to entering the service. The seriousness of this problem is attested by the fact that in one report² it is stated that 90 per cent of the patients with ulcer were discharged from the British Army. A similar report¹⁰ stated that about 50 per cent were invalided from the Royal Navy. As yet, we have no data on the influence of combat on the production of ulcer in our services.

Certainly many physicians will agree that under proper conditions patients who have peptic ulcer are capable of performing many important tasks, even though such duty may be limited. If these patients cannot tolerate the army or navy ration without recurrence of symptoms, they are promptly invalided from the service.³ Flood⁴ has stressed the fact that soldiers with peptic ulcer who are retained in the army should be of stable personality, because those with a neurotic temperament fare badly.

In the navy, since highly trained men are such a valuable asset, manage-

* Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

† On leave of absence from the Mayo Clinic.

ment of the patient with peptic ulcer, with the thought of returning him to duty, cannot be overemphasized. The evidence is ample that peptic ulcer is a difficult problem in the naval service, especially aboard ships, because naval service affords little opportunity for the physiologic gastroduodenal test that is the essential part of the nonsurgical treatment of ulcer. Every ocean voyager knows of the hypermotility and hypersecretory action of the stomach and duodenum which are called seasickness. In most instances symptoms of ulcer without complications among new recruits in the navy were present prior to enlistment. Since most of these men are young (from 18 to 25 years of age), few in this group should be considered as candidates for surgical procedures. Hence, experience has shown that it is advisable to discharge such men from the service before six months^{*} have elapsed from their enlistment, or the government becomes responsible for their continuous treatment and disability pensions.

On the other hand, officers and enlisted men whose ulcers have developed during their period of active duty are entitled to pensions and continuous medical or surgical treatment. Should they, too, be retired or be invalided from the service because of their ulcers? The indications for operation differ little in these cases from those in cases in civilian life. There seems to be an impression in the naval service that even if such patients are operated upon most of them will have to be assigned to shore duty (limited duty). This requires that an officer first be retired from active service and then recalled as a retired officer for limited duty. We believe, on the contrary, that a large majority of these patients who have active, chronic or recurring ulcers may be returned to active duty at sea or foreign stations even in the combat zones of operation, preferably partial gastrectomy, is performed as soon as the diagnosis is established. Consequently we have operated upon a selected group of those encountered at a base hospital in the last six months and returned most of them to active duty for a therapeutic trial. This, therefore, is essentially a preliminary report since we have operated upon only thirteen such patients in the past six months. Although eleven (85 per cent) have returned to active duty, it will be necessary to have a series of at least 100 cases, and to follow these for a year or more, before any definite decision can be arrived at concerning the results of the operation from the standpoint of the ability of the patient to perform active duty as a part of the navy after operation.

REPORTS FROM THIRTEEN UNITED STATES NAVAL HOSPITALS

In order to broaden the scope of the preliminary report, we have sought information from many of the larger naval hospitals in this country to determine the attitude of other medical officers on the ulcer problem among naval personnel. Special emphasis was placed on the percentage of patients thought to have a lesion requiring surgical measures, the operation performed, and the subsequent clinical course.

* Recently changed to three months

PEPTIC ULCER IN THE NAVY

TABLE I
INCIDENCE OF PEPTIC ULCERS AMONG BRITISH MILITARY AND NAVAL PERSONNEL
ADMITTED TO HOSPITALS BECAUSE OF DYSPEPSIA

Authors	Type of Hospital	Total Cases	Peptic Ulcers Per Cent	Gastric Ulcers Cases	Duodenal Ulcer Cases	Per Cent of Gastric and Duodenal Ulcers
Wade	Naval	1003	17	67	404	86
Brockbank*	Military	931	42.5	52	275	84
Morris	Military	500	50			
Parry and Newman	Army	287	89	42	164	80
Maringot	General	256	56	15	128	89
Graham and Kerr	Military	246	64.3	20	135	85
Spillane	Military	200+	32	10	54	84
Allison and Thomas	Naval	100	45	6	34	85
Wilcox	General	41	69	7	19	73
		Total—3564	55	219	1213	85

* Includes one case of carcinoma and nine of gastro enterostomy in which there was no precise evidence of the site of ulcer

TABLE II
TYPE AND TREATMENT OF PEPTIC ULCER
(Collected Series)

Type of Ulcer	Total	Treatment Cases	
		Surgical	Medical
Gastric	112	23	89
Duodenal	1219	72	1147
Gastric and duodenal	21	8	13
Total	1352	103	1249

TABLE III
DISPOSITION OF PATIENTS WITH ULCER AFTER TREATMENT
(Collected Series)

Disposition	Total	Surgical Patients	Medical Patients
Active duty	654	53	601
Limited duty	131	20	111
Discharged*	567	30	537
Total	1352	103	1249

* Of the total number listed as discharged and retired from service 137 had actually been transferred for further disposition two were still under treatment and three had died

We have had reports of 1,352 patients with proved peptic ulcer who entered thirteen United States naval hospitals from December 1, 1940, to December 1, 1942 (Table II) * One thousand two hundred and forty-nine

* The cooperation of the following commanding officers and their associates is greatly appreciated. The information collected by them and their suggestions have been freely used in this paper. U. S. Naval Hospital, Portsmouth, New Hampshire, J. T. Bennett, Pensacola, Florida, W. W. Hargrave and L. M. Nelson, Newport, Rhode Island, G. F. Thomas, Quantico, Virginia, P. M. Albright and W. M. Sheppe, Long Beach, California, L. D. Powell, Seattle, Washington, F. F. Murdock, Key West, Florida, J. W. Allen, Chelsea, Massachusetts, G. F. Clark and G. E. Cummings, Norman, Oklahoma, L. B. Marshall, National Naval Medical Center, Bethesda, Maryland, John Harper and W. T. Gibb, Jr., Balboa, Canal Zone. The Commanding Officer, Pearl Harbor, T. H., J. J. A. McMullin and C. E. Watts, Portsmouth, Virginia, Daniel Hunt and Michael Lake, Corpus Christi, Texas, R. R. Gasser, Mare Island, California, J. P. Owen and E. L. Markthaler, Corona, California, H. L. Jensen

TABLE IV
SURGICAL TREATMENT
(Collected Series)

Operation	Total
Resection with Polya type of anastomosis	39
Billroth I resection	9
Gastro enterostomy	8
Local excision	12
Other types*	36 ⁺
Total	103

* Most of these are closures of acute perforations

TABLE V
NUMBER AND DISPOSITION OF PATIENTS PREVIOUSLY OPERATED UPON FOR PEPTIC ULCER
WHO ENTERED HOSPITAL WITH RECURRENT ULCER OR OBSTRUCTION

Type of Treatment	Cases
Surgical	16
Medical	47
Total	63
Disposition	
Active duty	18
Limited duty	6
Discharged*	39
Total	63

* Of the number discharged, one died

(92 per cent) of these patients were treated medically and 103 (eight per cent) surgically. Seventy-one per cent of the 103 patients treated surgically were returned to duty, 53 to active, and 20 to limited duty (Table III). Fifty-five per cent of those treated medically were returned to duty. In about half of the surgical cases partial gastrectomy was performed, and in approximately a third simple closure of an acutely perforated ulcer was employed (Table IV). Of the 63 patients who had had previous operations for ulcer 25 per cent underwent another operation for recurring ulceration, with or without obstruction. Seventy-five per cent were treated medically. Thirty-eight per cent of these 63 patients were returned to duty (Table V). Ninety per cent of the 1,352 patients had duodenal ulcers, eight per cent gastric ulcers, and two per cent gastric and duodenal ulcers. The high percentage of duodenal ulcers (90 per cent) is in accord with the average 85 per cent reported by current British writers (Table I).

In the collected series from the United States naval hospitals, the reasons generally listed for discharging patients treated surgically from the service was their inability to tolerate a general diet. Of those treated medically, and later discharged, the reasons were listed as follows: (1) Disease existed prior to enlistment (E P T E) in a young recruit, (2) history of many recurrences, (3) symptoms not relieved and surgical intervention refused, (4) repeated hemorrhages, and (5) accompanying severe functional disturbances.

MANAGEMENT

Surgical Measures—The reasons for choosing surgical treatment for naval patients with peptic ulcer are essentially the same as those for civilian

patients In our series of 13 cases surgical treatment was advised for (1) repeated hemorrhages, (2) pyloric obstruction, (3) perforation, or (4) frequent recurrences, with progressive symptoms in spite of medical treatment Partial gastrectomy with a posterior Pólya-type of anastomosis, was performed in 85 per cent of the cases, in one case gastro-enterostomy was performed because technical difficulties prevented gastric resection, in one case of perforated duodenal ulcer simple closure was, at the time, the procedure of choice

The importance of making an early decision as to the type of treatment to be employed and the disposition of the patient cannot be overemphasized If surgical treatment is indicated, the earlier the operation is performed and the patient returned to duty, the better Since all these patients are hospitalized, there is a tendency to delay this decision until the patient has become so accustomed to hospitalization that he is reluctant to return to combat duty, regardless of the result of treatment In our group of 13 cases in which operation was performed only two patients were invalided from the service One was an officer who had spent a total of 14 months in various hospitals undergoing several courses of medical treatment before operation was advised Although the surgical result was physiologically and clinically excellent, the long period away from duty and the mental attitude developed by prolonged hospitalization and limitation of activities both physical and dietary were sufficient to produce a functional failure in two months after his return to active duty The second patient had a good result from operation, but was discharged because of an incapacitating war injury

Medical Measures—The medical treatment of peptic ulcer in the navy is essentially the same as that employed in civil practice, but the various duties to which the naval personnel are assigned after leaving the hospital make this nonsurgical form of treatment difficult Irregular hours, inadequate meals, seasickness, great exertion, great fatigue, and the nervous strain and apprehension over real and impending battle are a great hindrance to medical management Medical treatment, therefore, is advised only when symptoms are extremely mild and of short duration, and complications are not present

Aboard large ships, because of special messes and privileges, officers who have ulcers have a better opportunity for adequate medical management than enlisted men do For this reason every opportunity is given them to return to duty if their ulcer is responsive to the usual treatment, if it is not responsive surgical intervention is advised We have observed 35 patients with proved gastric or duodenal ulcer at a naval base hospital in this country during the past six months Twenty-two were treated medically, 16 (73 per cent) of these were returned to duty and six discharged Of the six discharged, three were advised to have operations because of complications, but refused, the other three had medical conditions other than ulcer requiring discharge

Our patients with ulcer have cooperated well, and almost all have been anxious to return to duty Those who responded to medical treatment did

so in the manner usually expected in civilian practice. This is in contrast to the experience of Flood, who observed that in the army, a large number of patients continued to complain of discomfort even after long periods of adequate treatment. Many of our patients have experienced dangerous and strenuous action, and date their gastro-intestinal symptoms from that period of mental and physical stress and strain. A large percentage of these patients quickly become free of symptoms, simply with rest and proper food at regular intervals. Those who lose their symptoms quickly and evidence desire to return to duty are returned without restrictions, others, less sure of themselves, who experience occasional dyspepsia are returned to limited duty ashore, those who have serious complications are advised to have an operation. Time and experience will determine the success of this policy but in view of the increasing need of trained manpower this program seems justified.

FURTHER STUDIES ON THE ULCER PROBLEM

It is fairly obvious that further study of treatment of ulcer among men in the navy is indicated. At present, we are not concerned with young recruits who have ulcers that existed prior to enlistment (E P T E). Such patients are discharged from the service because medical treatment cannot be carried on with any degree of satisfaction and yet they do not have sufficient trouble so that surgical procedures can be advised. When the ulcer is incurred during the period of the active service, however, it is important to treat the patient in such a way that he may return to duty if possible. This is particularly important if the patient is an officer, or a specialist who has become a real asset to the service.

Several problems must be solved in these cases. The first is whether repeated medical treatment is advisable. Of 537 patients in the collected series medically treated and discharged from service because of ulcer, 25 per cent had repeated periods of hospital treatment for their ulcer. The chances of those in this group of responding to medical treatment so that they become useful to the service is exceedingly doubtful. The second problem is the need of follow-up studies to determine the results of surgical treatment in the naval service. In our series, 37 per cent of the patients were treated surgically, 85 per cent of whom we returned to duty. In the collected series, only eight per cent were treated surgically, of whom 71 per cent were returned to duty. These results should be compared with those of conservative medical treatment. Seventy-three per cent of the patients in our series treated by medical measures only and 55 per cent of the patients in the combined series treated by medical means, returned to duty. These figures suggest that surgical treatment, when indicated, deserves wider use.

As previously mentioned, 25 per cent of the patients treated medically who were discharged from the service had been hospitalized repeatedly because of ulcer. It seems possible that surgical treatment should be employed more extensively in this group of cases.

To evaluate the final results of surgical treatment will require a follow-up study to determine (1) the time spent on the sick list, (2) ability to stand active and limited duty, and (3) a comparison of both medically treated and surgically treated patients to determine whether the radical treatment by gastric resection is warranted.

Certainly, from the results shown herein, there is, we believe, justification for radical surgical treatment of naval patients who have chronic, recurring, gastric or duodenal ulcers which develop during service. Officers and enlisted specialists with such ulcers, whose knowledge, experience and ability in naval activities make them particularly valuable to the navy, and the 25 per cent of medically treated patients who are discharged from the service because of chronic recurring ulcers, are the particular patients, we believe, that should be given the benefits of surgical treatment with the hope and expectation that their valuable services can be retained. However, until a much larger series of naval patients are operated upon, and observed subsequently as regards their reaction to naval duty, the advisability of surgical treatment of naval personnel who have gastric and duodenal ulcers in order to return the patients to duty cannot be determined definitely.

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DISCUSSION—COLONEL ROBERT H. KENNEDY, M.C. (New York). My commanding officer, up to a recent time, General Kirk, was extremely regretful that he could not be here. At the time that the preliminary program was received he asked our Chief of Gastro-Intestinal Section to prepare some data relevant to the paper of Captain Walters, and since he went away he wrote asking me to assemble this material and discuss the subject in his absence. This was prepared by Major Charles M. Caravati.

At the Percy Jones General Hospital, between January 15 and May 1, 1943 (the hospital opened on January 15) there have been 835 total medical admissions, of whom 69 were peptic ulcer patients.

Admitted to the Gastro-Intestinal Service were 108, 58 of whom were proven ulcers on that service. There were 11 more ulcers on the officers' ward (Table I)

TABLE I
THE ULCER PROBLEM AT PERCY JONES GENERAL HOSPITAL
(January 15 to May 1 1943)

	No of Cases
Total medical admissions	835
Total number of peptic ulcer patients	69
Total admissions to G. I. Service	108
Total proven ulcers on G. I. Service	58
Total admissions to Medical Officers Ward	125
Total proven ulcers on Medical Officers Ward	11

The diagnosis has been accepted by an attempt to follow the following criteria

- 1 Careful perusal of the clinical story
- 2 Complete roentgenologic studies, with repeat examinations when indicated
- 3 Gastric secretory studies, including night acid curves
- 4 Examination of three specimens of stool for occult blood
- 5 Critical review of the psychic status of the patient
- 6 Response to therapy
- 7 Gastroscopic examination

(1) *Clinical History* There were only a small percentage of patients in which the clinical history was not at least suggestive of peptic ulcer, who were later proved to have ulcer. However, in three individuals, the finding of a definite ulcer crater, which disappeared under treatment was demonstrated though the history, in no way pointed to the presence of same. Ninety to 95 per cent of soldiers proven to have ulcers gave a history suspicious of same existing prior to entrance into the service. This agrees with reports of other army hospitals—Chamberlain of Lawson General, reporting 90 per cent, Thomas of Fort Meade Station Hospital, 93 per cent, and Berk at Tilton General, approximately 90 per cent. Eight cases had had a history of acute perforations. Eight had gross but not massive gastro-intestinal hemorrhages. None of these were admitted during the acute stage of their hemorrhages. There was only one case of gastric ulcer in this series. Other series, in the Army and Navy, have reported an incidence of four to eight per cent of all peptic ulcers occurring within the stomach. Fifty-two of the 69 soldiers with ulcer, had seen overseas service. Ninety per cent of these gave histories indicative of the presence of ulcer prior to their entrance into the Army. The one case of perforation which occurred on our service had returned from overseas eight days previously.

(2) *Roentgenologic Examination* In a small percentage of cases, clinical evidence and the roentgenologic findings did not agree. At times the clinician expected a roentgenologic report of duodenal deformity when the Roentgenological Department reported negative findings. The variability of the roentgenologic evidence of ulcer was forcefully pointed out in an analysis of some of these cases. The presence of a crater, with deformity, was considered definite evidence of an ulcer, usually active. Deformity, without a crater, but with a niche, or marked duodenal irritability, also was considered to indicate probable presence of an ulcer. Absence of irritability, with the presence of deformity, and with the absence of subjective symptoms, was most often interpreted as a probable healed ulcer.

(3) *Gastric Secretory Study* Study of gastric secretion was accepted, using three methods

- (a) Quantitative study of the basal secretion
- (b) A study of the acid curve after alcohol stimulation, and after histamine, when there was no free acid after oral alcohol
- (c) Study of the night acid curve (aspirations every two hours)

A study of the gastric secretion of this group, using alcohol as a secretory stimulus reveals that there appears to be less hypersecretion in this group than in most cases reported from civilian life. It has been formerly taught that the free acid level is usually

higher in this age-group than in a comparatively older group, and in this series of cases, over 50 per cent of the proven cases of ulcer showed normal acidity curves

(4) *Occult Blood in Stool* It is regrettable that, due to faulty laboratory technic, our findings are probably incorrect. In no case was the presence of occult blood reported positive before April 15th, but since that time several cases have been positive, after a change in technical procedure was adopted in the laboratory

(5) *Psychic Study* A critical review of the psychogenic status of each patient indicated that a marked neurogenic element was present in a very large percentage of soldiers with duodenal ulcer. Psychic trauma often appeared to act as a "trigger" mechanism, apparently reactivating a dormant lesion. It was the opinion of most observers that activation of the epigastric distress which was prominent in many soldiers returning from overseas to the mainland, and which was not apparently related to seasickness, was best explained on the basis of anxiety, incident to the hazardous sea voyage through heavily submarine-infested waters. The diet did not impress us as being unsatisfactory

(6) *Response to Therapy* Conservative medical management consisting of an adequate, bland, low roughage diet, with frequent interval feedings made up chiefly of milk, crackers and juices, was adhered to in all cases except the very acute. In the latter group which comprised only a few patients, they were placed in bed and given milk and cream at two-hour intervals during the 24 hours, with aluminum hydroxide frequently. All other cases were treated ambulatory except two with pyloric obstruction, in which Wangensteen suction and aluminum hydroxide drip were used alternately. Each patient was given ascorbic acid 100-200 mg t i d. Tincture of belladonna was administered to all in whom there appeared to be evidence of hypertonus. Several patients were placed solely on olive oil

Results Regardless of the routine followed, all patients reacted uniformly well to simple but intense medical management. The average length of time from admission, to relief of symptoms was less than four days. Many were relieved within 24 hours. No case of proven uncomplicated ulcer failed to receive relief within ten days under management as above described, except one who had an acute perforation while under a milk and cream regimen, and was bedfast

(7) *Gastroscopic Examination* Twenty-five returned overseas soldiers with duodenal ulcers were gastroscoped, six showing positive findings. Five of these represented gastritis, and one edema. Of those showing gastritis, four were of the superficial type and one of the atrophic type. All were very mild, in fact, it was the impression of the Endoscopists that in only one of these cases was the pathologic change sufficient to cause clinical symptoms. These examinations were conducted without previous aspiration of the stomach, in order to eliminate the factor of trauma from the interpretation of the findings

The positive diagnosis of ulcer now requires that a soldier be separated from the Service, except in the case of married officers, who may be recommended for limited duty if they can be stationed at a post where they may live at home and follow a satisfactory dietary regimen as ordered

CAPTAIN WALTERMAN WALTERS, M C, U S N R (closing) I should just like to say a word, in closing, regarding the large number of men who are being discharged from the armed forces because of chronic gastric and duodenal ulcer. As I said in my paper, there certainly is no indication to operate upon young men of 18 to 25 years of age who have had symptoms which existed prior to enlistment. Most of these men do not have complications unless they perforate, which few of them do

On the other hand, from my reasoning, I can see no reason why, if the operation of partial gastrectomy has given the excellent results that it has in patients with surgical ulcers who required operation for several years, such results cannot be expected when a similar type of operation is performed under similar indications upon men, and valuable men, in the armed forces, and that is a particular reason why Doctor Butt and I were carrying on this study

The need for such a study is emphasized by the fact, also, that in this collected series of 1352 patients with proven ulcer reported, from several Naval hospitals, in only eight

per cent of those cases had surgical procedures been carried out. Yet, in the very small group of cases which we reported, we carried out surgical procedures in 37 per cent of the cases.

Now, there is only one way that one is going to determine whether or not a surgical procedure is advisable in Naval personnel who have surgical ulcers, and that is to perform a sufficient number of operations upon a sufficient number of patients in whom surgical treatment is indicated, and give them therapeutic trial duty, at home and abroad, and see what the results are. I personally believe that it will show that about the same results can be expected as obtain in similar operations upon civilians, namely, that probably 80 per cent of those patients can eat anything and do anything, and that is one particular reason for this paper.

EFFECTS OF PEDICLE GRAFTS OF JEJUNUM IN THE WALL OF THE STOMACH ON GASTRIC SECRETION¹

EXPERIMENTAL AND CLINICAL STUDIES

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EXPERIMENTS which have been carried out in our laboratory have revealed the fact that when a pedicle graft of jejunum is implanted in the wall of the stomach profound effects are produced on gastric secretion^{1, 2, 3}. It is with such effects and their possible employment in the treatment of peptic ulcer that this paper deals.

Methods—Healthy mongrel dogs were used for these experiments which consisted in the resection under nembutal anesthesia of an area of the anterior wall of the stomach approximately 4 x 6 cm in size and about midway between the cardia and pylorus, and the implantation into this defect of a pedicle graft of upper jejunum with its circulation intact. This was obtained by isolating a segment six centimeters in length which was then opened along its antemesenteric border and fastened in place by means of interrupted sutures of silk. The continuity of the jejunum was restored by end-to-end suture.

The gastric secretion of each animal had been examined after 24 hours' fast at least once before the beginning of the experiment. In the first few animals the gastric analyses were carried out under light nembutal anesthesia, but this was found to be unnecessary and, although it appeared to have no appreciable effect on the secretion, was abandoned for simple analysis using animals trained to tolerate a small stomach tube. At the time of operation direct measurements of the p_H of the surface of the mucosa at seven different areas in the stomach were made by inserting electrodes of the Beckman p_H meter through the defect in the anterior wall just prior to the implantation of the jejunal graft. Subsequent analyses were carried out in a similar fashion and p_H determinations were made from 45 minutes to two years and six months after the implantations, inserting the instrument through a gastrotomy.

Control animals were subjected to anesthesia and operations of similar length, as well as to resection of an area of the gastric wall and closure of the defect without a graft.

Twenty-five animals subjected to this procedure, in one form or another

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have been studied, 19 having had gastric analyses, 13 p_H measurements, and six being investigated by both methods. A summary of the results is set forth in Figures 1 and 2. Of the 13 animals in which the p_H studies were carried out after the implantation of a jejunal graft, 12 showed a rise in the average hydrogen ion concentration of seven regions of the gastric

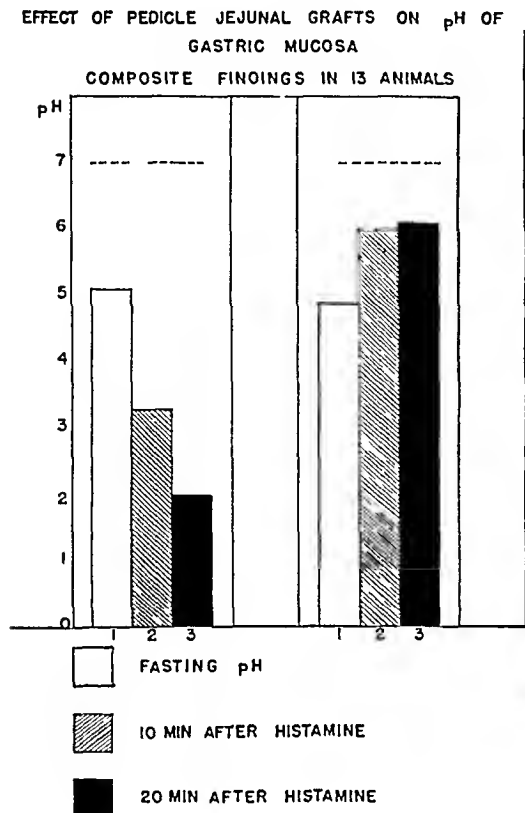


FIG 1

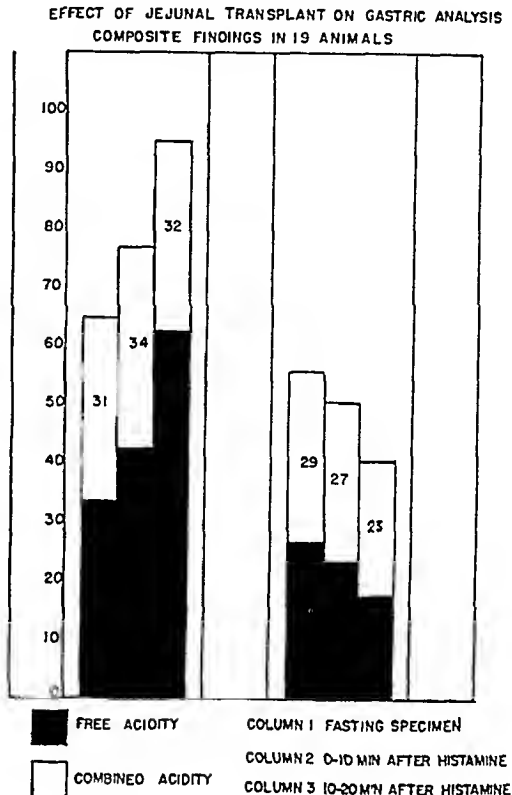
FIG 1—Effect of pedicle jejunal grafts on p_H of gastric mucosa

FIG 2

FIG 2—Effect of jejunal transplant on gastric analysis

mucosa following the administration of histamine in contrast to the findings before operation. In the remaining animal this reversal did not occur, but the fasting p_H was 6.7 compared to a preoperative level of 5.4 and the fall after histamine was considerably less marked.

In the group of 19 animals in which gastric analyses were performed the average fasting free and total acidity was definitely lowered after operation and following the injection of histamine these values declined progressively in 17. In one of the remainder the rise after histamine was comparatively small and the p_H studies of the gastric mucosa were at variance with the gastric analysis—the former showing a definite rise of p_H . In only one animal was there evidence of increased acidity after histamine, in both the gastric analyses and p_H studies following operation. When the graft in this dog was investigated it was found to be the seat of circulatory disturbances, the mucosa being markedly congested and superficially ulcerated.

There were numerous adhesions about the pedicle. This graft, the only one by the way to show such disturbances, was resected and a fresh graft implanted, following which the usual findings after jejunal graft supervened.

While this animal is included in the series summarized in Figures 1 and 2, the result was a decided exception, and, inasmuch as it was corrected by reoperation, seems to have been due to an error in technic. It does serve to emphasize, however, the need for most meticulous regard for the circulation of the graft when it is implanted.

It appears, therefore, that in these animals the implantation of pedicle jejunal grafts in the wall of the stomach has tended to lower the fasting acidity and has reversed or considerably diminished the normal rise in acidity following the injection of histamine. In all but one instance in which the average p_H of seven regions of the gastric mucosa was studied the normal fall in p_H following histamine was converted into a rise in this value.

As to the time of their development, these changes vary somewhat even in the experimental animals, the p_H changes coming on in some as early as 45 minutes after implantation of the graft, while in others, for no apparent reason, these as well as the alterations in acidity in the gastric analysis may be delayed for several weeks. The alterations persist for as long as we have kept animals which is now more than two and one-half years.

In two dogs, when the effects of the transplant were established, it was then resected and further p_H measurements carried out. These indicated that within one hour one animal showed the normal response to histamine, although the fasting p_H remained slightly higher than before the graft was implanted. In the other the p_H of the gastric mucosa and its reaction to histamine corresponded to the normal findings in all respects.

In order to compare the reaction of the animals subjected to this operation to some secretory stimulus other than histamine injected intramuscularly, a modification of the method of Bloomfield and Keefe,⁴ employing alcohol as the secretagogue, was used.

Method—Dogs of both sexes were used after having received no food for 24 hours. Following the aspiration of a fasting specimen of gastric juice, 50 cc of seven per cent alcohol was administered and allowed to remain in the stomach for ten minutes. The entire contents of the stomach was then aspirated, 20 cc was withheld and the remainder replaced in the stomach. Ten and 20 minutes later the same procedure was repeated. All specimens were titrated with 0.1 normal NaOH in the usual manner.

In Figure 3 the results of this test in five normal animals are compared with those in seven with pedicle jejunal grafts. It will be seen that the marked increase in acidity which followed the instillation of alcohol in the controls is almost completely lacking after the implantation of pedicle jejunal grafts.

Having established the fact that pedicle grafts of jejunum produce these effects the question quite naturally arises as to whether grafts from

other levels of the tract possess similar properties. A series of animals were, therefore, assembled, three with transplants from the transverse colon, three with ileal, four with duodenal and five with jejunal grafts, and the gastric analyses and mucosal pH after histamine compared with

those in five normal animals. These studies indicate that the property of depressing gastric acidity is confined to grafts from the jejunum and duodenum with the former possessing somewhat greater activity (Figs 4 and 5).

Since gastro-enterostomy is so frequently effective in relieving symptoms of peptic ulcer, it would seem important to compare the secretory effects of this operation with those following implantations of a pedicle jejunal graft. To this end the following series of experiments were carried out.

After preliminary gastric analyses, six dogs were operated upon and the response of the pH of the gastric mucosa to histamine determined in the manner described above. Following this, an anterior gastro-enterostomy was performed and a period of from one to three weeks permitted to elapse, at the end of which time these determinations were repeated.

The bowel about the gastro-enterostomy stoma was then converted to a pedicle graft by dividing the jejunum approximately two centimeters proximal and distal, and inverting toward the stoma beneath mattress sutures of medium silk. The continuity of the intestine was then reestablished by end-to-end anastomosis.

The results of these experiments are shown in Figures 6 and 7. In each instance, gastro-enterostomy failed to modify materially the response to histamine as it appeared in the gastric analysis, whereas, after the conversion of the bowel about the stoma to a pedicle graft the histamine response was reversed in all animals and the fasting free acidity markedly lowered in all but one.

In five out of six, gastro-enterostomy failed to prevent a marked diminution of the average pH of the mucosa of seven different regions of the stomach after histamine, but following conversion to a pedicle graft the pH rose progressively when histamine was administered.

EFFECT OF PEDICLE JEJUNAL GRAFT
ON GASTRIC ACIDITY FOLLOWING ALCOHOL

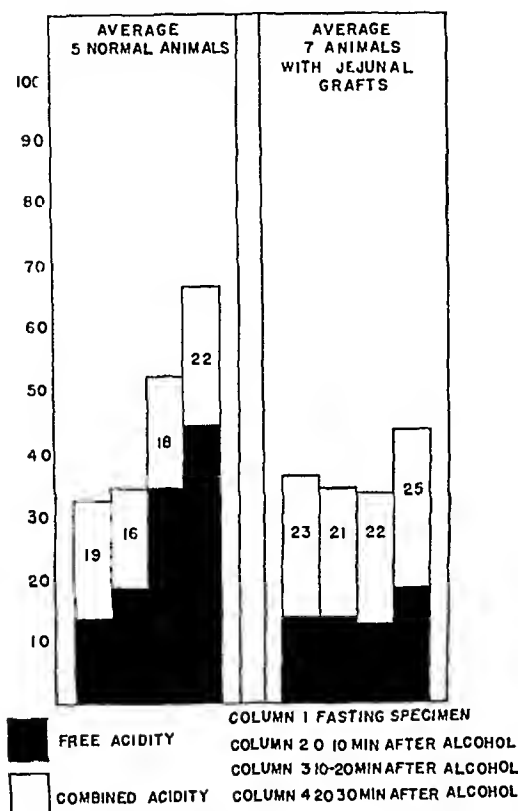


FIG. 3.—Effect of pedicle jejunal graft on gastric acidity following alcohol

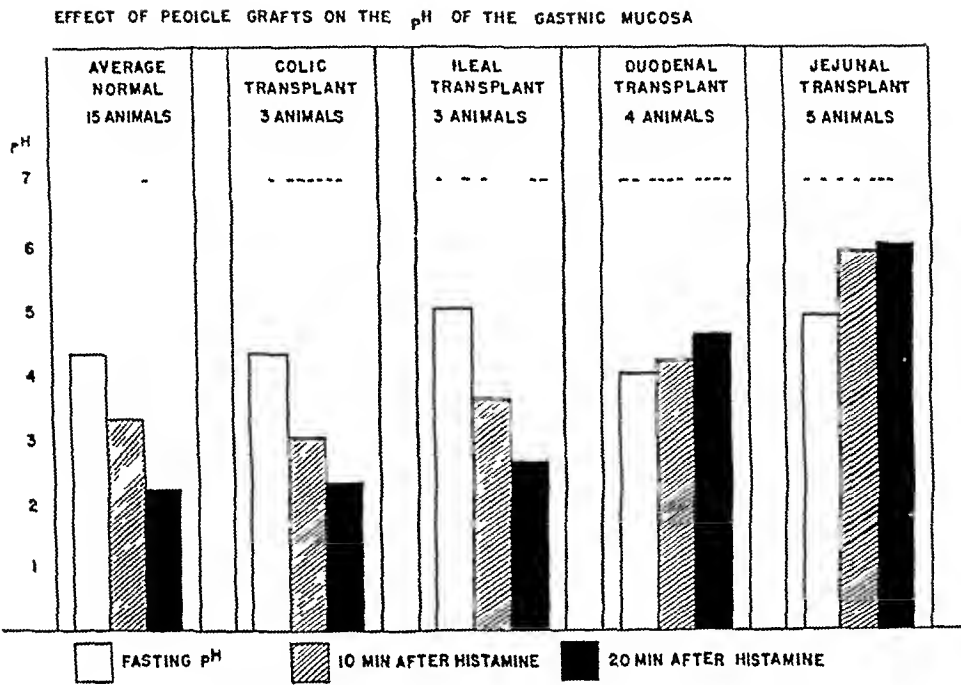


FIG 4—Effect of pedicle grafts on pH of the gastric mucosa

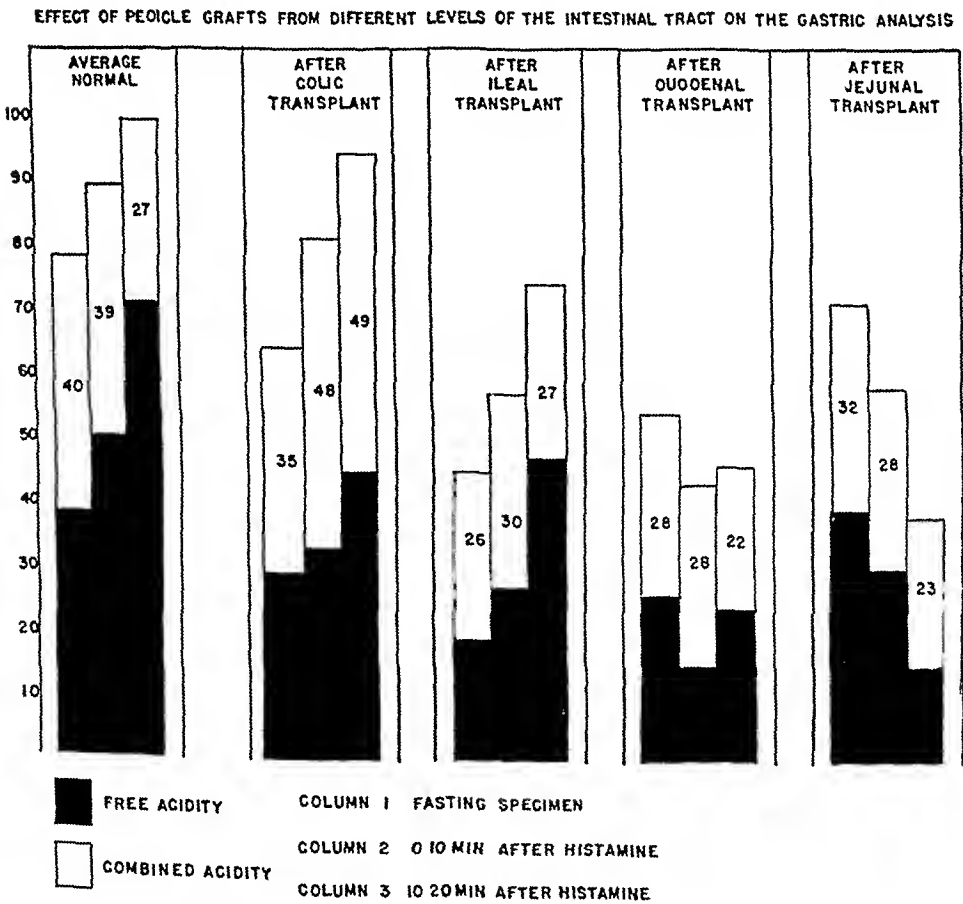


FIG 5—Effect of pedicle grafts from different levels of the intestinal tract on the gastric analysis

The jejunal washings were found to be of pH 5.9 to 6.5 and to contain practically no titratable buffer, as the pH was altered by three points when one drop of N/10 HCl or N/10 NaOH was added to five cubic centimeters of the washings

As controls, eight animals, Series II, including the five used as recipients in the experiments, were subjected to one or more routine gastric analyses, and additional analyses, Series III, exactly comparable to those used to test the jejunal washings except that saline alone was instilled, were carried out in eight animals including Nos. 1925 and 2072 of the experimental series

While the specimen removed at the end of the ten-minute period during which the jejunal washings remained in the stomach always showed a marked reduction in acidity it seemed possible that the factor of dilution with an indeterminate portion of the 25 cc of material instilled might have influenced the result, and for the comparison with the control series this specimen was therefore discarded

The comparative results in the experimental and control series appear in Table I. From these figures it is apparent that while the injection of one milligram of histamine is followed by a considerable rise in both the free and total acidities in both of the control series, there is a definite fall in each of these values when the injection follows the instillation into the stomach of washings of isolated jejunal loops. By the end of 20 minutes the effect of the instillation has worn off to some extent (Fig. 6)

Recognizing that the facts so far presented indicate that pedicle jejunal grafts exert definite effects in lowering qualitatively the acidity of the gastric secretion, it remains to be shown whether the reduction is also quantitative, and whether the effects are produced through neutralization of gastric juice or actual inhibition of secretion. Evidence bearing on these points is available from several sources. First, the data on the pH of the gastric mucosa indicate inhibition rather than neutralization, particularly since it can be

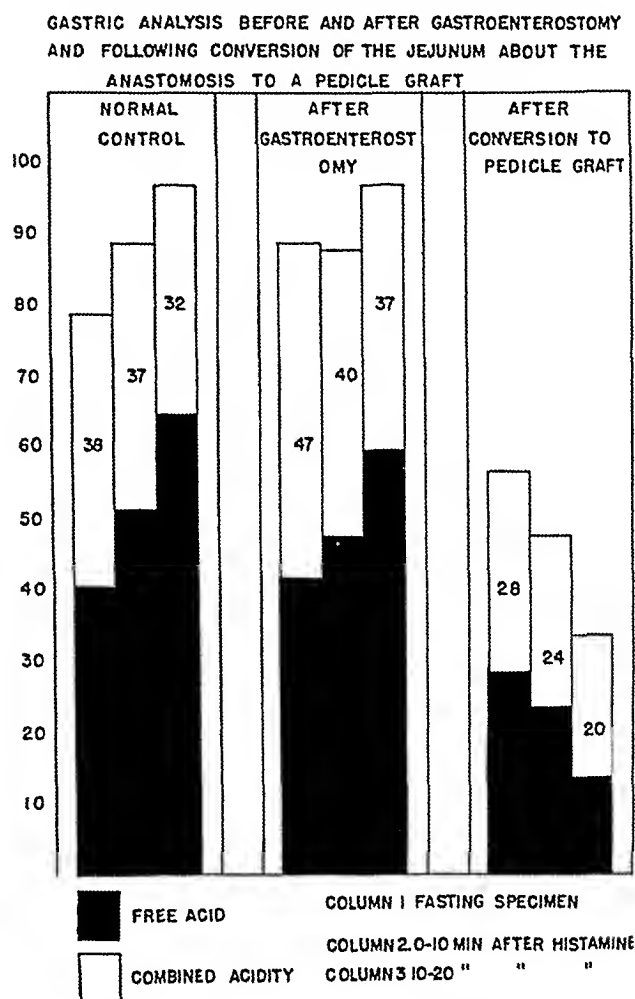


FIG. 6—Gastric analysis before and after gastroenterostomy and following conversion of the jejunum about the anastomosis to a pedicle graft

demonstrated that the changes take place even when the pylorus is completely obstructed. The same impression is gained by noting in the gastric analysis the total milligrams of acid secreted and the concentration per cubic centimeter. Reference to Table II, containing the data concerning the gastric secretion in ten typical experiments, shows that the total amount of HCl secreted, which normally increases considerably following the administration of histamine, remains at or below the fasting level in animals with jejunal grafts. Obviously the concentration of acid as measured in milligrams per cubic centimeter follows the figures for the total acidity.

TABLE II

GASTRIC SECRETORY FINDINGS BEFORE AND AFTER IMPLANTATION OF PEDICLE JEJUNAL GRAFT
COMPLETE DATA IN TEN CONSECUTIVE EXPERIMENTS

ANIMAL NO	Before Operation									After Operation								
	Vol. Fasting			0-10 min after Hist			10-20 min after Hist			Vol. Fasting			0-10 min after Hist			10-20 min after Hist		
	C.C.	F.	T.	C.C.	F.	T.	C.C.	F.	T.	C.C.	F.	T.	C.C.	F.	T.	C.C.	F.	T.
1909	5	60	90	8	72	106	15	80	108	7	28	58	10	22	52	6	10	38
1917	4	45	105	9	60	110	10	64	116	8	24	44	10	20	40	5	4	22
1954	6	58	80	5	42	86	12	56	96	12	26	64	5	8	64	6	12	48
2013	18	40	68	22	52	82	19	76	96	10	34	54	16	0	46	22	32	44
1986	12	20	48	19	52	60	14	50	72	13	32	64	21	20	30	29	10	16
2115	19	22	38	14	52	48	26	64	82	5	0	16	8	0	12	24	5	2
2106	5	0	14	7	2	18	16	38	60	7	18	38	14	12	34	9	8	22
2077	11	16	26	15	14	40	12	40	78	23	40	66	18	44	70	36	52	54
2119	33	58	58	30	0	18	25	44	62	8	22	60	26	20	56	31	20	50
2161	19	46	80	16	64	94	29	88	104	17	40	66	15	0	6	18	0	4
Averages	12.7	32.5	60.6	14.5	57	66.2	17.6	58.9	87.4	13.9	26.4	53	14.2	19.6	41	18.5	13	31.8

Following Figures are Derived from Average of Above Ten Animals

mgm HCl	28.11	35.04	56.14	26.90	21.24	21.46
mgm HCl/cc	2.21	2.42	3.19	1.99	1.50	1.16
Parietal Secretion	4.69	5.84	9.36	4.46	3.54	3.58
NonParietal Secretion	8.01	8.66	8.24	9.44	10.66	14.82

Some very interesting information in this connection is obtained by estimating the activity of the acid-secreting cells by the method used by Gray, Bradley and Ivy.⁵ This is based on the statement of Lui, Yuan and Lim,⁶ and on that of Hollander,⁷ that the secretion of the oxyntic cells contains approximately six milligrams of HCl per cubic centimeter. Thus, by dividing the total milligrams of HCl secreted by six, one obtains a figure representing the volume of "parietal secretion", and by subtracting this from the total volume, an index of the mucous and pyloric or diluting secretion. While these figures cannot be considered as more than estimated, they do provide a rough gauge of the activity of these cells.

These values, as they appear in Table II, suggest, also, that the activity of the acid-secreting cells in response to histamine is definitely diminished following the implantation of a pedicle jejunal graft, while that of the remaining cells is somewhat increased.

The p_H of the mucosa of the graft itself has been between 6.1 and 6.9, and, as noted above, the secretion of comparable areas of jejunum in isolated

loops was always at about that level (5.9 to 6.5), and contained no appreciable buffer on titration.

Further evidence is also obtainable in the total chloride values which, while never increased after implantation of jejunal grafts, have on a number of occasions shown a marked decrease—proportional in some instances to the fall in acid secretion.

The burden of evidence suggests, therefore, that pedicle jejunal grafts implanted in the wall of the stomach also cause a quantitative reduction in the acidity and produce their effects chiefly by actual inhibition of the acid secretory mechanism—at least so far as its normal response to stimulatory effects of histamine or alcohol is concerned. Further than this, it would be unwise to go, based on experiments completed at present, but work now in progress is shedding additional light on the factors responsible and their mode of action.

Since it seems probable that gastric acidity, or something closely associated with it, is one of the important factors in the etiology and symptomatology of peptic ulcer, it occurs to one at once that such an operation as we are discussing should be tested in the laboratory both as to its influence in preventing the formation of ulcers produced under controlled experimental conditions and in the cure of such ulcers if, and when, produced.

Experiments of this sort were carried out, and the results have been reported.⁸ It was found possible to produce duodenal erosions or ulcerations uniformly in nine control animals through the injection of a histamine-beeswax mixture (Figure 9) after the method of Varco and his associates,⁹ whereas we were completely unable to bring about such changes in any of the three animals with pedicle jejunal grafts tested. The gastric analyses in such animals were also of interest, and the data from two animals with jejunal transplants and two controls are recorded in Table III. It will be seen that not only is the fasting free and total acidity markedly lower in the transplant animals than in the controls despite the prolonged exposure to histamine, but the normal response to the injection of one milligram of histamine is reversed. Such experiments present strong evidence of the efficacy of pedicle jejunal grafts in the wall of the stomach in preventing the formation of ulcers under strenuous experimental conditions and also in nullifying, in some way, the otherwise powerful effects of the prolonged administration of histamine on gastric acidity.

To test the curative effects of such grafts the histamine-beeswax mixture was administered to two animals until bloody stools were noted. They were then operated upon, and erosions in the duodenum similar to those seen in other animals observed through duodenotomy. This was then closed, and a pedicle jejunal graft implanted in the wall of the stomach. One animal died of bronchopneumonia 24 hours after operation but, in the other, autopsy three weeks later showed the duodenum (Fig. 10) to be completely normal, despite the fact that the administration of the histamine-beeswax mixture in the same dosage had been continued throughout its life.

TABLE III

COMPARISON OF GASTRIC ANALYSIS AFTER THE INJECTION OF 120 MG OF HISTAMINE PHOSPHATE DAILY FOR 30 DAYS, IN ANIMALS WITH AND WITHOUT PEDICLE JEJUNAL GRAFTS

	<u>Fasting</u>	<u>10 min after Histamine</u>	<u>20 min after Histamine</u>
Dog #1704 (Graft)			
Free	50	40	0
Combined	<u>38</u>	<u>32</u>	<u>25</u>
Total	88	72	25
Dog #1777 (Graft)			
Free	30	28	18
Combined	<u>30</u>	<u>24</u>	<u>22</u>
Total	60	52	40
Dog #1710 (Control)			
Free	70	70	102
Combined	<u>40</u>	<u>50</u>	<u>40</u>
Total	110	120	142
Dog #1801 (Control)			
Free	70	74	90
Combined	<u>38</u>	<u>40</u>	<u>30</u>
Total	108	114	120

pH OF GASTRIC MUCOSA BEFORE AND AFTER GASTROENTEROSTOMY AND FOLLOWING THE CONVERSION OF THE JEJUNUM ABOUT THE ANASTOMOSIS TO A PEDICLE GRAFT

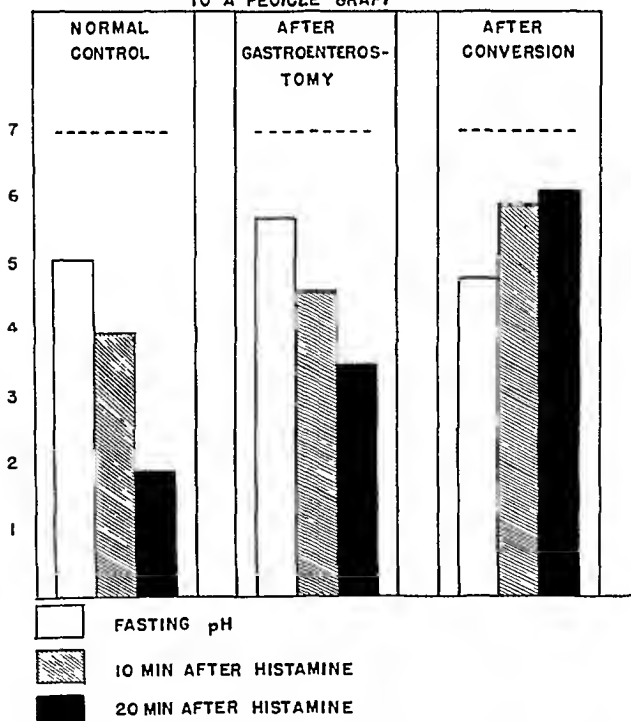


FIG 7—pH of gastric mucosa before and after gastroenterostomy and following the conversion of the jejunum about the anastomosis to a pedicle graft

A sample of gastric juice obtained at the time of duodenotomy in this animal showed fasting free acidity of 80°, and a total of 130°. Ten days after the implantation of the jejunal graft, and despite the continued administration of histamine, the fasting free acidity was 34°, and the total 62°, both values falling still further after the additional injection of one milligram of histamine phosphate intramuscularly. Further evidence of the influence of such grafts in healing ulcerated areas is seen in our experience with

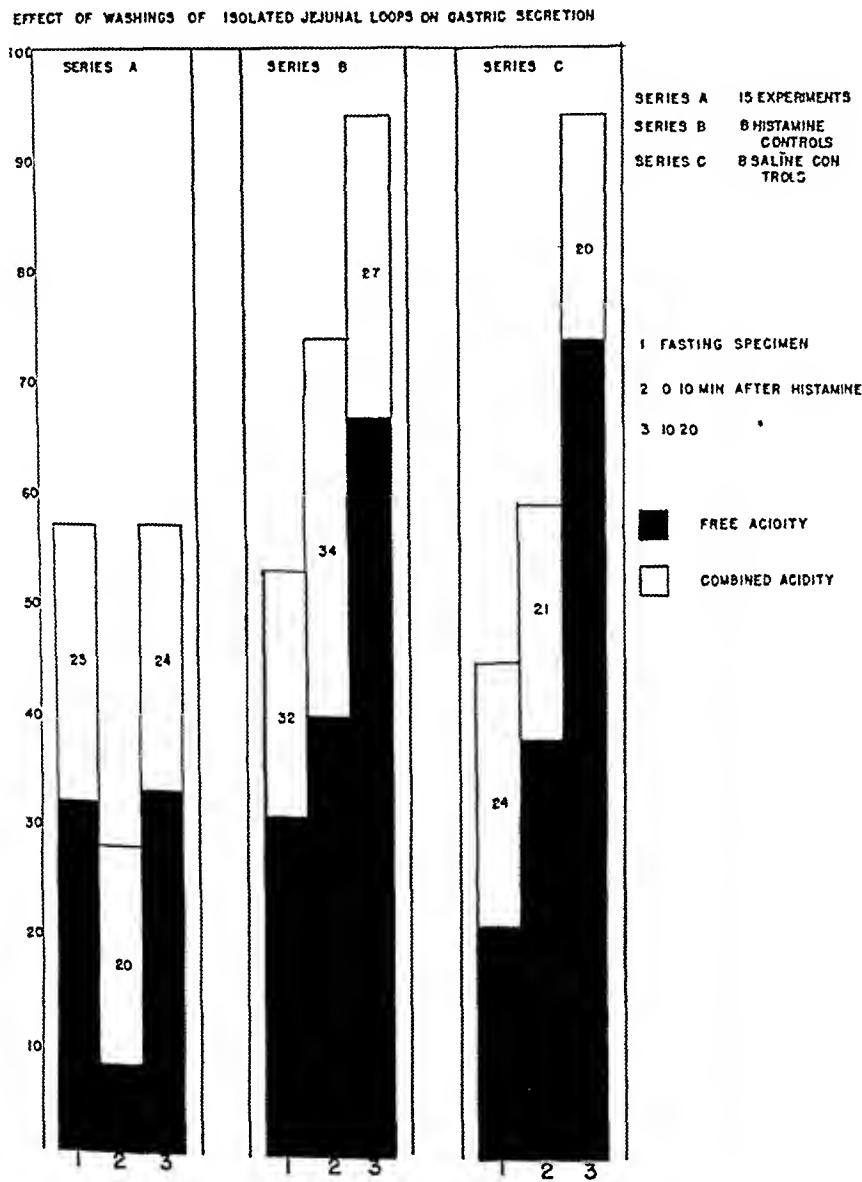


Fig 8—Effect of washings of isolated jejunal loops on gastric secretion

Pavlov and Heidenham-pouch animals. A number of these dogs developed ulceration about the external opening, which promptly healed when a graft was implanted in the wall of the pouch. However, despite the apparent correlation between the acid-inhibiting action of jejunal grafts and their preventive and curative effects in experimental ulcer in animals, we must be cautious in accepting this as the actual mode of action. As we know from follow-up studies in patients suffering from ulcer¹⁰ many patients are

completely cured, both symptomatically and objectively, despite acid values in the gastric analyses as high or higher than before operation

Such results in animals naturally suggest the application of the method in the elective operative treatment of peptic ulcer in man, but before discussing the results of such an application we must mention certain other experimental findings pertinent to the selection of cases and to the evaluation of the method. First of all, it has been demonstrated repeatedly in animals that in the presence of a gastro-enterostomy or pyloroplasty the inhibitory effect of the pedicle jejunal graft is lost. The reasons for such an effect are not clear, but, obviously, until this can be further clarified it would exclude from consideration for operation all cases with organic pyloric obstruction. In addition, we have excluded cases of duodenal ulcer with any marked bleeding as unsuitable, at least until the efficacy of the method shall have been better established. We are left for the present, therefore with two main indications. First, the group of uncomplicated ulcers which have resisted prolonged medical treatment, and, second, cases of marginal ulcer following gastro-enterostomy, without pyloric obstruction. It may be that further investigations will extend these indications, but it has seemed wise to limit the procedure to these groups, for the time being at least.

In the group of marginal ulcer following gastro-enterostomy, the operation is particularly useful, as it is much less of a procedure than the dismantling of a gastro-enterostomy followed by resection. In these cases the gastro-enterostomy is taken down, the edges of the gastric side of the anastomosis excised, and a pedicle jejunal graft implanted into the defect.

Soresi,¹¹ in 1915, reported the use of pedicle grafts of ileum in the plastic repair of pyloric stenosis due to ulcer in 18 cases, without a death, as well as in 11 instances of defects of the stomach and intestines with only one leak. Although his proposals are purely from the point of view of plastic procedures and, as we now know, since the ileum was used, could not have had the effect noted with jejunal grafts his report serves to indicate the possibility of survival of such a graft.

Our experience in animals indicates that if due care is taken to assure an adequate blood supply to the graft, it survives and is tolerated very well. This confirms the work of Dragstedt and Vaughn,¹² who implanted grafts from various levels of the intestinal tract and from other organs, into the stomach to study their survival and the effect of the normal gastric secretion upon them, finding that all such grafts survived without evidence of pathologic alteration when their circulation was intact. This resistance to digestion by hydrochloric acid-pepsin mixture in the gastric juice in normal concentration is an attribute shared by many tissues when their nutrition is normal.

It may properly be asked, however, whether such grafts can survive, without injury, the effects of abnormal gastric secretion such as is met with in the presence of peptic ulcer. The only evidence which we have bearing on this point is the fact that such a graft has survived when implanted

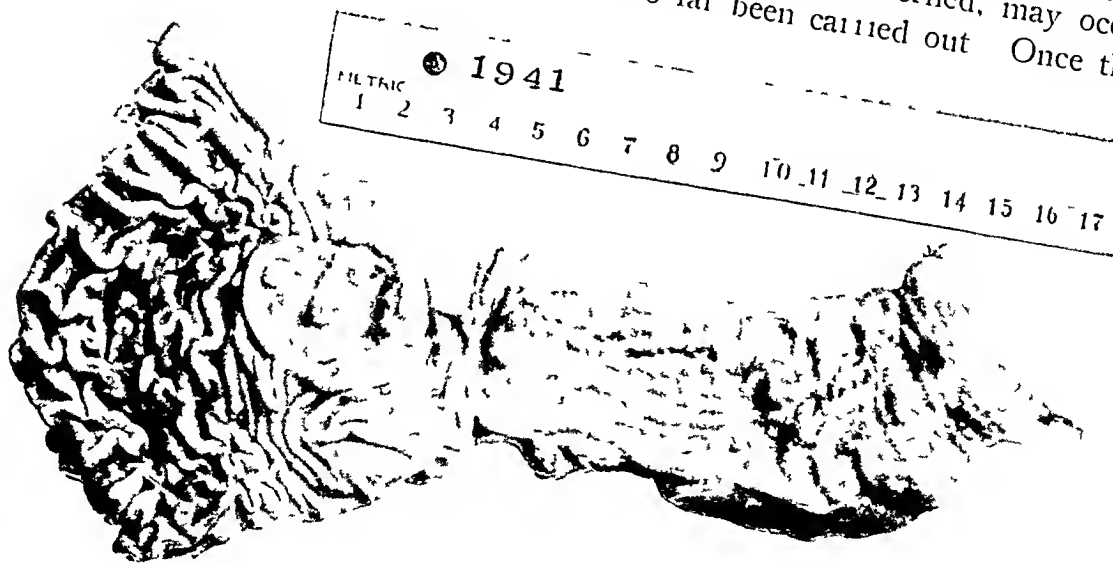
JEJUNAL GRAFT IN STOMACH



Fig 9—Photograph of experimental duodenal ulcer in a dog produced by the administration of 1.0 mg of histamine phosphate daily

into the stomach of an animal with a fasting free acidity of 80°, and a total acid of 130°, due to the prolonged administration of a histamine-beeswax mixture. In addition roentgenologic studies of the patients operated upon show the grafts to be intact from three weeks to three months after implantation.

The risk would seem greatest during the first few weeks after the graft is implanted and when the ulcer is still unhealed, as our studies in patients with ulcer indicate that a period of both quantitative and qualitative hypersecretion, at least so far as the hydrochloric acid is concerned, may occur temporarily after the operation as it has so far been carried out. Once this



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Fig 10—Photograph of duodenum and pylorus in a dog in which duodenal erosions produced by histamine disappeared after the implantation of a pedicle jejunal graft

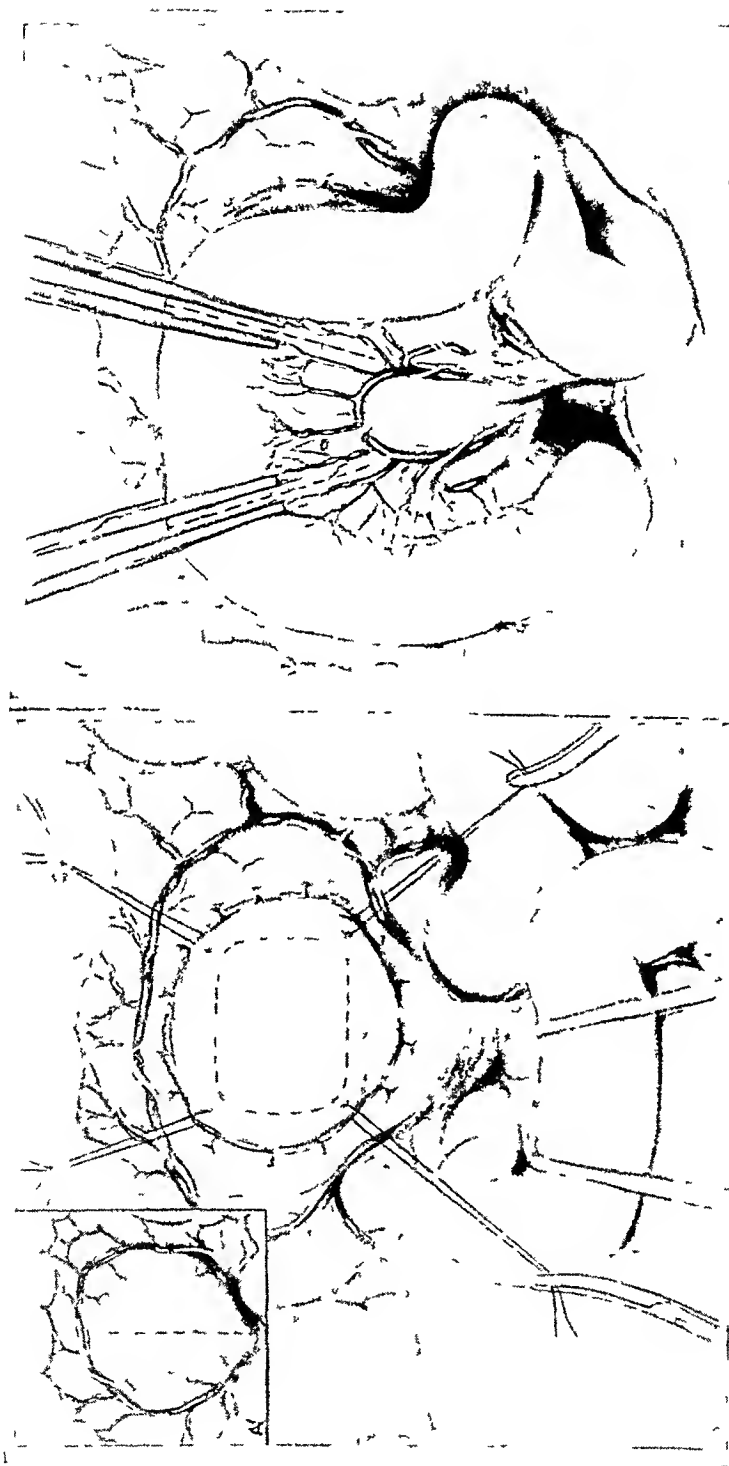


FIG 12

FIGS 11 17—Illustrating the steps in the operative procedures

FIG 11

is past, however, the risk should be markedly reduced as the effect of the graft is to maintain the acid at a lower level and to modulate materially any tendency to rise as the result of various stimuli. This must be taken into consideration in evaluating the results of this operation in clinical cases of ulcer.

The operation as performed in clinical cases has been essentially the same as that in animals, with minor modifications. The steps in the procedure are as follows:

TECHNIC OF OPERATIVE PROCEDURES

(1) Either an upper left rectus or a transverse incision across the epigastrium gives adequate access to the operative site. After elevating the transverse colon, a vertical incision is made just to the left of the middle colic artery and extending from the base of the mesocolon upward as far as is safely possible. Through this opening the posterior wall of the stomach is delivered and the edge of the mesocolon sutured about an area some ten centimeters in diameter. Four traction sutures are placed in the wall of the stomach at the angles of the site in which the graft is to be implanted (Fig. 11).

(2) The selection of the donor site for the jejunal graft is, we believe, one of the most important steps in the entire operation, not because the property of influencing the gastric secretion appears to be confined to any narrow segment of jejunum but because great care must be taken to select an area in which the distribution of vascular supply is such as to assure adequate circulation to the graft after transection of the bowel and the mesojejunum as far down as the arching branches of the superior mesenteric vessels. Since these latter course in the mesojejunum from two to five centimeters from the bowel, an incision between the shorter branches, as indicated in Figure 12, gives an adequate pedicle for the graft.

(3) When the appropriate site has been selected, usually about 25 to 30 cm. from Treitz' ligament, this segment of jejunum is isolated by dividing between pairs of Kocher clamps. The continuity of the intestine is restored by bringing together the proximal and distal clamps caudad to the graft and performing an end-to-end anastomosis using mattress sutures of silk (Fig. 13).

(4) The Kocher clamps are now removed from the isolated segment which is approximated at a point on its superior surface about one centimeter from the antemesenteric border to the lower or lesser curvature edge of the site previously selected in the posterior wall of the stomach, using a continuous suture of silk (Fig. 14).

(5) The isolated jejunal segment is now opened by excising approximately 15 cm. of its circumference at the antemesenteric border and all bleeding points carefully ligated with No. 00 plain catgut (Fig. 14 inset).

(6) An area corresponding to the size of the opened segment of jejunum is now excised from the posterior wall of the stomach one border being

FIG 13

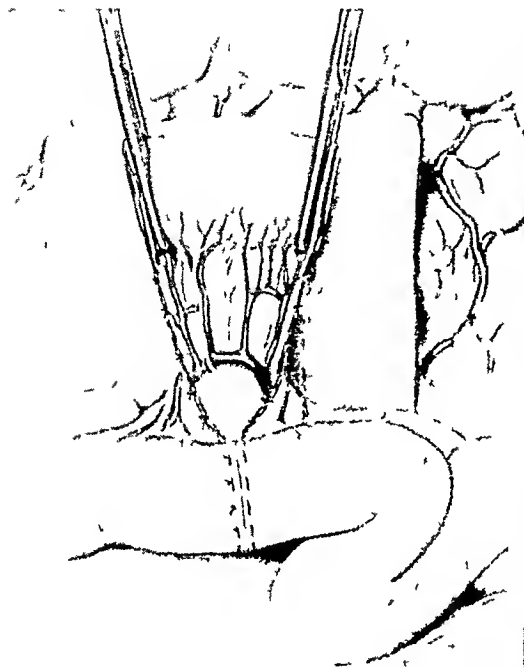


FIG 14

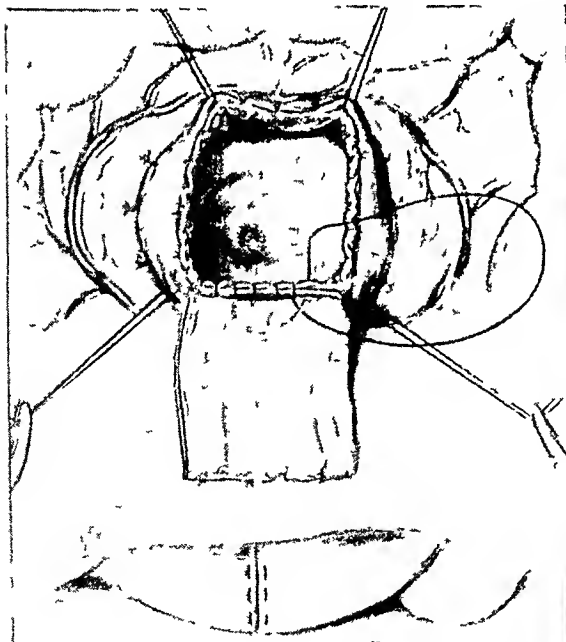
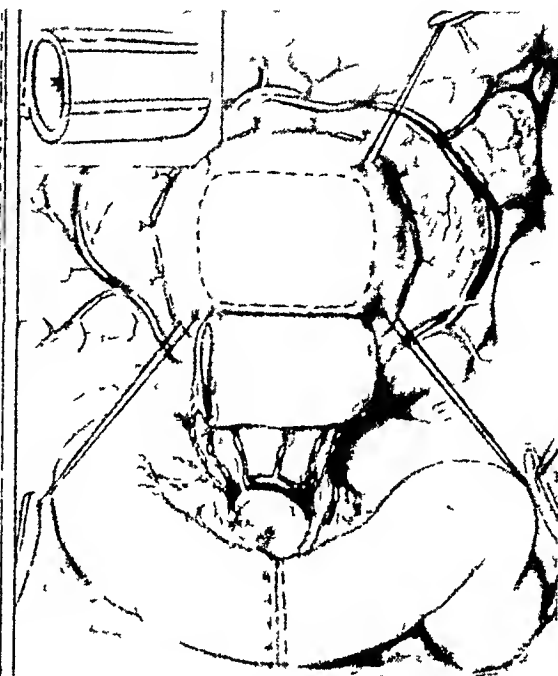


FIG 15

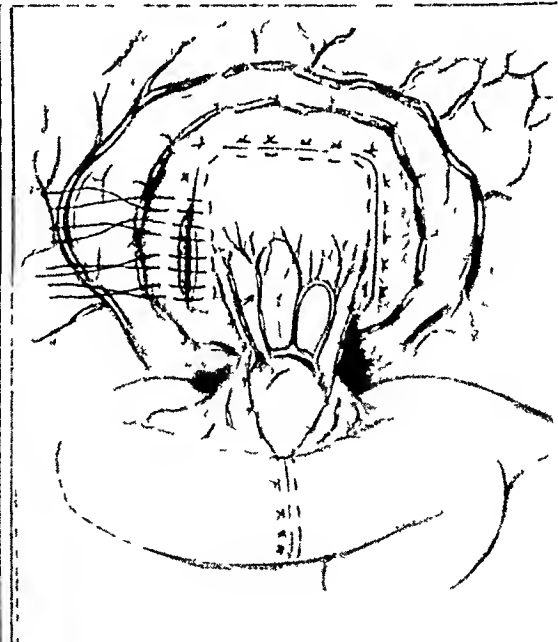


FIG 16

FIGS 11-17—Illustrating the steps in the operative procedure (Cont)

along the superior margin of the pedicle graft. A continuous lock-stitch of No. 1 chromic catgut is placed as reinforcement of the continuous silk suture (Fig. 15).

(7) The remaining edges of the graft are approximated to the borders of the defect in the gastric wall by means of mattress sutures of silk (Fig. 16).

(8) The bowel, just proximal and distal to the end-to-end anastomosis, is now tacked to the wall of the stomach at the site of the graft, and two serosal sutures of fine silk placed between the edges of the mesojejunal defect at the site of anastomosis and the edges of the mesenteric pedicle of the graft (Fig. 17). This is done to prevent the jejunum, when filled, from exerting traction at an angle on the pedicle of the graft.

CASE REPORTS

Case 1—N. Y. H. History No. 270902. V. G., a 20-year-old girl, was admitted to the New York Hospital because of recurrent epigastric pain of five years' duration. Two and one-half years previously an active duodenal ulcer was demonstrated roentgenographically. The symptoms at first responded to medical treatment but recurred, and, despite a careful dietary regimen, became much worse during the two months prior to admission. There had never been any vomiting nor any bleeding from the gastro-intestinal tract. Roentgenologic examination just before operation revealed the duodenal cap to be definitely defective with distinct crater formation. The secretory studies before operation are shown in Table IV.

TABLE IV
GASTRIC SECRETORY FINDINGS BEFORE AND AFTER IMPLANTATION OF PEDICLE GRAFT IN PATIENT V. G. (CASE 1)

Gastric Analysis	January 29, 1943								March 8, 1943							
	Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist		Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist	
	Vol.	11°F	Vol.	63°F	Vol.	90°F	Vol.	99°F	Vol.	11°F	Vol.	15°F	Vol.	13°F	Vol.	12°F
	40 cc	5°C	15 cc	5°C	20 cc	9°C	22 cc	14°C	36 cc	10°C	20 cc	10°C	16 cc	10°C	24 cc	10°C
		16°T		68°T		99°T		113°T		21°T		25°T		23°T		22°T
mgm HCl	23.36		37.23		72.27		90.73		27.59		18.25		15.43		19.27	
mgm HCl /cc	584		2.48		3.61		4.13		77		91		84		80	
Parietal Secretion	3.89		6.21		12.05		15.12		4.60		3.04		2.24		3.21	
NonParietal Secretion	36.11		8.79		7.95		6.88		31.40		16.96		13.76		20.79	
Total Cl ME/L	85		117		109		156		94		89		88		73	
Neutral Cl	69		49		10		23		73		64		65		51	
Total Cl x Vol	3400		1755		2180		2992		3384		1780		1408		1752	

At operation, February 1, 1943, an ulcer was found in the duodenum, with a crater approximately one centimeter across. This was surrounded by an area of induration some four centimeters in diameter. A pedicle jejunal graft was implanted in the posterior wall of the stomach by the technic described above.

The postoperative course was entirely unremarkable, and all the ulcer symptoms

have been completely relieved. She was discharged from the hospital on the 19th postoperative day, and returned to her work as a typist six weeks after operation. Report of the roentgenograms taken on the 17th postoperative day states: "In contrast to previous examinations, in which the duodenal cap always appeared defective, the films on this occasion showed it to be entirely normal in size and shape. This certainly suggests marked improvement" (Fig 18).

The gastric analyses since operation have shown a gradual decline in free acidity after histamine—this value reaching 82° one week after operation, 66° on the 19th day, and 15° on the 35th day. The secretory findings five weeks after operation are shown in Table IV. During the intervening period, these figures trended steadily downward and have remained at or about the low level since that time. In this case, also, the evidences of diminished activity of the acid secretory mechanism is striking. These appear in the total chloride values before and after operation and in the total milligrams of hydrochloric acid secreted during 30 minutes after the administration of one milligram of histamine phosphate intramuscularly, which amounted to 200.23 mg just before operation, and was only 51.95 mg five weeks later. In the interval, this patient, like the others which we have been able to follow closely, had a considerable quantitative hypersecretion, although the gastric juice secreted contained less free and total acid.

The result in this patient has been excellent in the three and one-half months during which she has been observed. When seen on May 5, 1943, she had gained 15 pounds in weight, and her gastric analysis showed no free HCl in the fasting specimen, with a rise to only 15° 30 minutes after histamine. The total HCl secreted in the same period was only 19.69 mg.

Case 2—N Y H History No 324713 V Z a 50-year-old white, married, Lithuanian electrician, who had had symptoms of duodenal ulcer for three years. This pain had been accentuated with hunger, and at first was relieved by taking soda. His habits made dietary treatment of the ulcer impossible, as he indulged freely in both alcohol and tobacco, and he was, therefore, admitted to the hospital. Roentgenologic studies showed a defective duodenal cap and evidence of duodenitis (Fig 19). Examination also revealed hypertensive cardiovascular disease, benign prostatic hypertrophy and hepatomegaly. The gastric secretory findings before operation are shown in Table V. He was placed on a strict dietary regimen, with powders, but as his symptoms continued operation was decided upon.

At operation, March 1, 1943 a large ulcer was found located on the superior and posterior surface of the duodenum. The crater would easily admit the tip of the forefinger, and was surrounded by an area of marked induration. A pedicle jejunal graft was implanted by the usual technique.

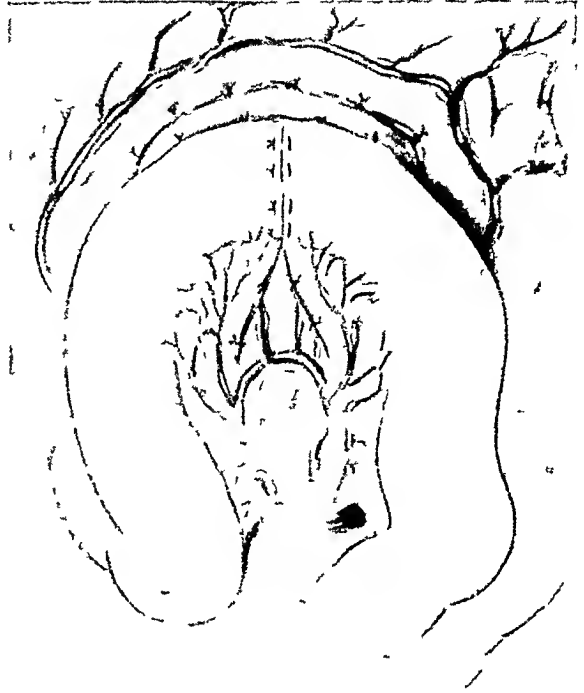


FIG 17

FIGS 11-17—Illustrating the steps in the operative procedure (Cont.)

JEJUNAL GRAFT IN STOMACH

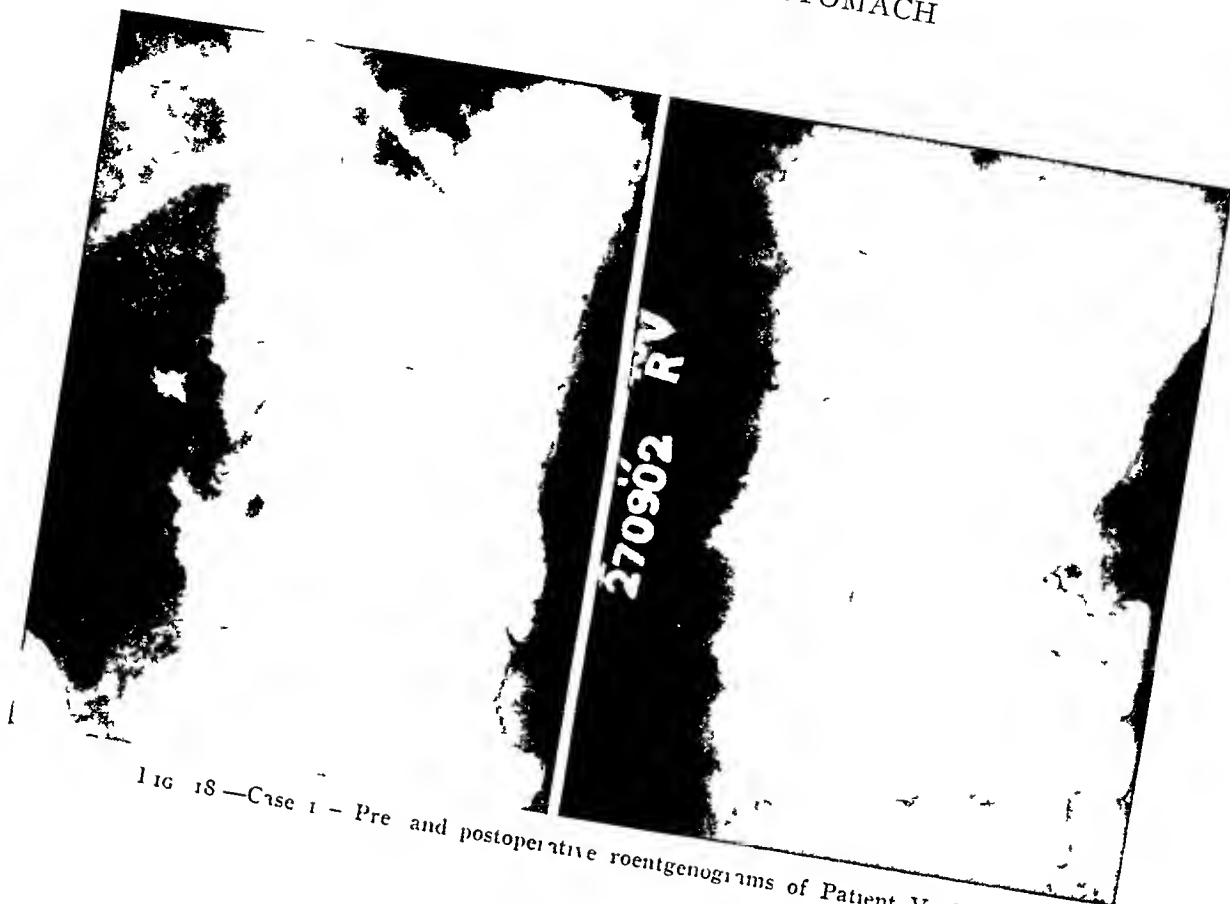


Fig 18—Case 1—Pre and postoperative roentgenograms of Patient V G

TABLE V
GASTRIC SECRETORY FINDINGS BEFORE AND AFTER IMPLANTATION OF PEDICLE GRAFT IN PATIENT V Z
(CASE 2)

March 9, 1943										May 3, 1943									
Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist		Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist					
																Vol	°F	°C	T
Vol		Vol		Vol		Vol		Vol		Vol		Vol		Vol		Vol		Vol	
55 cc		45 cc		35 cc		30 cc		87 cc		24 cc		23 cc		31 cc		31 cc		31 cc	
18°F		19°F		16°F		11°F		13°F		11°F		10°F		11°F		11°F		11°F	
18°C		19°C		16°C		11°C		13°C		11°C		10°C		11°C		11°C		11°C	
18°T		19°T		16°T		11°T		13°T		11°T		10°T		11°T		11°T		11°T	
mgm HCl		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc		mgm HCl /cc	
36 14		96 91		113 70		104 03		104 79		79 71		106 61		144 83		144 83		144 83	
66		2 15		3 25		3 47		1 20		3 31		4 64		4 69		4 69		4 69	
6 02		16 15		18 95		17 34		17 47		13 26		17 77		24 16		24 16		24 16	
48 98		28 85		16 05		12 66		69 53		10 74		5 23		6 84		6 84		6 84	
83		122		140		145		86		136		155		155		155		155	
65		63		51		50		53		45		28		27		27		27	
4565		5490		4900		4350		7482		3264		3565		4805		4805		4805	

Following operation, he was completely relieved of his symptoms, and was discharged on the 17th postoperative day. Nine weeks after operation he had gained 25 pounds in weight, was still symptom-free, and was anxious to return to work. Although the gastric acidity fluctuated somewhat, there has been a definite reduction, and the findings on the latest analysis, nine weeks postoperative, are shown in Table V. Here, it will be seen that not only are the values for free and total acidity considerably reduced, but the same trend is reflected in the total chlorides of the gastric juice.

Case 3—N Y H History No 318194 C F, a 52-year-old, white, married American clerk, was first observed in the Out-Patient Department and complained of severe epigastric pain coming on two hours after meals, which was relieved by eating. These symptoms had been present intermittently for two years before he was admitted to the hospital for the first time in May, 1942. On that occasion, he was much relieved by diet, and was discharged after one week, and was referred to the Out-Patient Department. The symptoms recurred in January, 1943, and increased

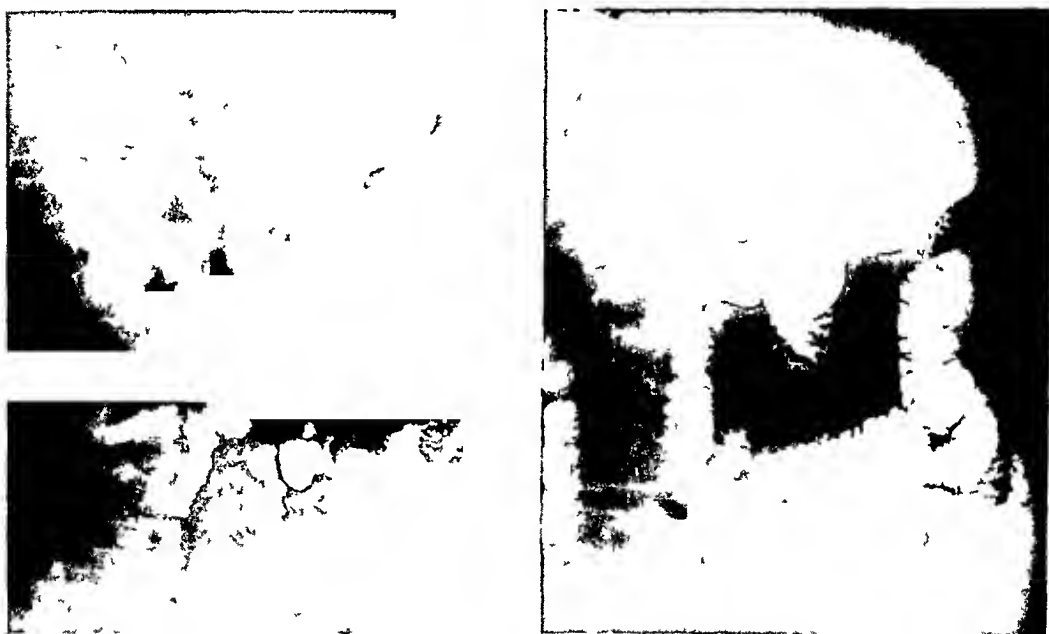


FIG 19—Case 2—Pre and postoperative roentgenograms of Patient V Z

in severity despite intensive medical treatment. On this occasion, there was considerable tenderness and some voluntary spasm in the epigastrium. Roentgenograms, March 15, 1943, revealed a large duodenal cap with a good-sized ulcer at the base. Physical examination revealed generalized arteriosclerosis, with hypertension. Gastric secretory findings before operation showed fasting free and total acidity values of 25° and 46°, respectively, rising to 79° and 96° within 30 minutes after histamine.

At operation, March 19, 1943, the upper abdomen was found to be the site of numerous fibrous adhesions in which the pylorus and first portion of the duodenum were buried. However, it was possible to palpate an ulcer on the posterior duodenal wall, with a definite crater. Considerable difficulty was experienced in elevating the transverse colon because of the adhesions, and the mesocolon was markedly shortened. The posterior aspect of the stomach was also the seat of many adhesions which had almost obliterated the lesser peritoneal sac. These were eventually severed, and the operation performed as outlined.

His postoperative course was entirely smooth, and he has been free of any symptoms referable to his ulcer. Incomplete gastric analysis, ten days after operation, showed

JEJUNAL GRAFT IN STOMACH

the free acid values to be considerably lower than before. Further studies have been impossible thus far, as the patient left town before these could be undertaken.

The result in this case has been good as far as symptoms are concerned, but until further information can be obtained, the effects of the procedure on gastric secretion must be considered as uncertain.

Case 4—N. Y. H. History No. 324166. L. G., a 47-year-old colored woman had had epigastric distress after meals for nine years, which had been treated by diet and Sippy tablets. This pain was intermittent in character, and was accentuated on taking fried or fatty foods. Roentgenograms showed an active duodenal ulcer. The gastric secretory findings are shown in Table VI. The patient was placed on a modified Sippy regimen, with powders, and kept on strict bed rest. This failed to relieve her symptoms, however, and operation was decided upon.

TABLE VI

GASTRIC SECRETORY FINDINGS BEFORE AND AFTER IMPLANTATION OF PEDICLE GRAFT IN PATIENT L. G. (CASE 4)

Gastric Analysis	February 25, 1943								May 4, 1943							
	Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist		Fasting		0-10 min after Hist		10-20 min after Hist		20-30 min after Hist	
	Vol	0°F	Vol	22°F	Vol	39°F	Vol	55°F	Vol	29°F	Vol	27°F	Vol	30°F	Vol	28°F
	25 cc	3°C	30 cc	23°C	25 cc	21°C	20 cc	27°C	142 cc	11°C	23 cc	10°C	6 cc	8°C	94 cc	11°C
		3°T		45°T		60°T		82°T		40°T		37°T		38°T		39°T
mEq HCl	2.74		49.27		54.75		59.86		207.32		31.06		8.32		133.81	
mEq HCl/cc	11		1.64		2.19		2.49		1.46		1.35		1.39		1.42	
Parietal Secretion	46		8.21		9.13		9.98		34.55		5.17		1.39		22.30	
NonParietal Secretion	24.54		21.79		15.87		10.02		107.45		17.83		4.61		71.70	
Total Cl ME/L	90		104		118		135		104		97		97		85	
Neutral Cl	87		59		58		53		64		60		59		46	
Total Cl x Vol	2250		3120		2950		2700		14768		2231		582		7990	

At operation, March 24, 1943, a pedicle jejunal graft was implanted. Since operation her symptoms have been entirely relieved, but up to May 3, 1943, 40 days after operation, she had continued to show very high values for free and total acidity. Similar findings have been observed for as long a period in other cases, which have later shown a diminished secretion. It must, therefore, be said that, as of 40 days after operation, the symptomatic result has been good, but that studies of the gastric secretion must be continued before the ultimate result can be appraised.

SUMMARY AND CONCLUSIONS

1. Experimental work is presented which indicates that a pedicle graft of jejunum when implanted into the wall of the stomach produces profound effects on gastric secretion.

2. These effects consist in a reduction of the fasting free acidity and a marked diminution, or actual reversal, of the normal response of the gastric acidity to such secretory stimulants as histamine and alcohol.

3. Such effects are not produced by the ordinary gastrojejunostomy but

appear promptly when the bowel about the stoma is converted to a pedicle graft and the normal continuity of the tract reestablished

4 Grafts from the colon or ileum are without such action, while those taken from the duodenum are effective, but considerably less so than jejunal implants

5 The presence of the factor responsible can be demonstrated in saline washings of isolated jejunal loops, and accumulated evidence indicates that its effects are exerted by actual inhibition of acid secretion, at least so far as the response to histamine is concerned, rather than by neutralization

6 Pedicle jejunal grafts have been shown to be effective both in the prevention and in the cure of experimental ulcers produced in dogs by the prolonged administration of histamine phosphate

7 It has been found that the effects of a pedicle jejunal graft are lost in the presence of a gastro-enterostomy or pyloroplasty

8 The operation has been applied to patients with duodenal or marginal ulcer, with excellent immediate clinical results in all, and with gastric secretory changes in two of the three studied for a sufficient period after operation, which are similar to the alterations seen in the experimental animals. Since the third patient was the latest to be operated upon, it is entirely possible that similar changes may occur in her case

9 It is suggested that if subsequent work confirms these findings, this may constitute a new approach to the problem of the surgical treatment of peptic ulcer

10 This operation involves the transplantation of a portion of one organ of a physiologic system to a point elsewhere in that system, for the purpose of modifying the physiologic activity of the recipient organ. So far as we are aware, this utilizes a new principle in the field of surgery

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Note At the time of returning the proof of this paper the first four patients operated upon remain symptom free and have all resumed their occupations In addition, the operation has been successfully performed in six other patients The clinical and laboratory findings in this latter group will be reported at a later date

DISCUSSION—DR LESTER R DRAGSTEDT (Chicago) A new observation that throws fresh light on the pathogenesis or treatment of gastroduodenal ulcer is always welcome Most of the experimental studies of the past few years are in harmony with the concept that the cause of ulcer is excessive continuous secretion of gastric juice both during digestion and, more importantly, during the interdigestive phase The copious secretion at night, when the gastric glands are normally quiescent, is especially dangerous since the buffering effect of food is absent The cause of this abnormal continuous secretion has not been determined, and it is here that the studies of Dr Andrus, and his associates, seem to me to be very important If it is due to the continuous formation in the body of histamine or some similar chemical substance, then we should expect, on the basis of this experimental work, that the transplantation of a jejunal patch into the stomach would be a successful method of treatment On the other hand, if the continuous secretion is neurogenic in origin I should anticipate no beneficial effect I am inclined to favor the latter view In 1932, Mathews and I implanted segments of duodenum into the stomach of dogs Valves were placed in the pylorus to prevent the backward regurgitation of the duodenal secretions Under these conditions a typical perforating ulcer appeared in the duodenal transplant in one of the animals This would seem to indicate that the duodenal mucosa has less resistance to gastric digestion than the stomach mucosa While the situation in man may well be different from that obtaining in this experiment, nevertheless, it would seem prudent to watch these patients carefully for the possible formation of an ulcer in the jejunal transplant

DR J SHELTON HORSLEY (Richmond, Va) The work that was done by the authors is interesting I would like to ask whether they found that the substance which inhibited the secretion of acid in the stomach decreased in its potency from the duodenum down to the ileum, and also whether it would be possible to prepare from the mucosa of the duodenum or jejunum an extract which might be efficient in the treatment of peptic ulcer

Does the application of duodenal or jejunal mucosa to the stomach, as in pyloroplasty, or partial gastrectomy, or posterior gastro-enterostomy, simulate the transplantation of a graft from the jejunum to the stomach?

After the Billroth-I type of gastrectomy, when much of the stomach has been removed and the duodenum is flared open, it would seem that there would be ample contact between the duodenal mucosa and the stomach In what respect does the grafting of a segment of the jejunum, with its blood supply intact, differ from gastric operations in which the mucosa of the duodenum or jejunum is united to the mucosa of the stomach?

DR WILLIAM DEW ANDRUS (closing) The experimental work which we have carried on to date, although still incomplete, suggests that the substance responsible for these effects does not act as a hormone, that it is not enterogastrone, and that it differs

from the substances contained in extracts of mucosa of the jejunum, with the possible exception of the "biodialysate," of Walawski. Some features of the jejunal grafts suggest that histaminase may be the responsible agent, but so far such histaminase as has been available to us has not been effective when placed in the lumen of the stomach. However, I do not feel that this can be excluded as yet.

Further work is in progress on the nature of the effects of such grafts, their mode of action and their effects when secretory stimuli other than histamine or alcohol are used.

GASTRIC HISTOLOGY AND SUBTOTAL GASTRECTOMY^{*}

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THE PRESENT CONCEPTS of the gross and histologic features of "banal" gastritis are based almost completely upon data acquired from the study of resected specimens of the stomach. These became available with the adoption of partial gastrectomy as the operation of choice for gastric carcinoma and for many cases of gastric, duodenal, and jejunal peptic ulcer. The surgeon and pathologist previously hampered by the rapid postmortem changes which occurred in the gastric mucosa were now enabled, because of well preserved material, to accurately study the histologic nature of the changes in the mucosa of the stomach. Then, too, gastroscopy subsequently increased this growing interest, for it soon became necessary to correlate the gastroscopic findings with the actual histology of the gastric mucosa. Although isolated cases of simultaneous gastroscopic and histologic analyses could be found in texts and periodicals, no systematic study had been undertaken until recently, when several investigators studied the resected stomachs of patients who had been previously gastroscoped. A few observers studied microscopically the biopsies obtained through the gastroscope. Others, influenced by the findings in experimental animals attributed the gross and microscopic gastric mucosal changes to the ligation of the blood vessels and the action of acid upon such tissue deprived of its blood supply. Their conclusions, if true, would not only negate many of the accepted basic histologic concepts of gastritis, but would naturally exclude the resected stomach and duodenum as source materials.

This study was undertaken to determine whether any histologic alterations occurred in the stomach wall during the operation of subtotal gastrectomy. The group consisted of 35 ward patients upon whom this operation was performed. Duodenal ulcer was present in 25 patients, gastric ulcer in four, jejunal ulcer in three, peptic ulcer of the esophagus in one, and gastric carcinoma in two.

The preoperative treatment in all cases was essentially the same. The patients were deprived of food for 14 to 17 hours before operation. The stomach was gently aspirated and then lavaged with warm tap water by stomach tube four to six hours prior to operation. A Levine tube was then introduced, left *in situ*, and aspirated at intervals, so that a minimal amount of gastric secretion remained. Following anesthesia, the abdomen was opened and a biopsy was obtained from the anterior wall of the stomach approximately four centimeters proximal to the pylorus and two centimeters cephalad.

^{*} Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

to the greater curvature. In the earlier cases a rubber covered intestinal clamp was applied across the biopsy site in order to avoid contamination of the peritoneal cavity when the specimen was excised. This precaution was soon found to be unnecessary, so that in the majority of cases the anterior wall of the stomach in this region was gently elevated with forceps and a segment was excised with a minimal amount of trauma. The resulting gastric defect was then closed by an inverting continuous linen suture. Following this the vascular supply of the portions of the stomach and duodenum which were to be resected were ligated. The De Petz clamp was then applied proximal to the reentrant angle, the stomach was divided and the duodenum transected.

TABLE I

No. of Cases	Interval between Original Biopsy and Removal of Resected Specimen
10	10-20 minutes
9	20-29 minutes
6	30-39 minutes
3	40-49 minutes
4	50-58 minutes
3	Not recorded

TABLE II

No. of Cases	Interval between Removal of Resected Specimen and Fixation of Postresection Biopsy
30	1-5 minutes
1	6 minutes
2	10 minutes
1	15 minutes
1	35 minutes

The interval between the original biopsy and the gastric resection varied from 10 to 58 minutes (Table I). After the removal of the surgical specimen additional pieces of gastric wall adjacent to the original biopsy were excised (Table III). This site was chosen because gastritis produces only focal lesions in many cases, and any changes relative to the surgical procedure might be expected to be more intense around the previously traumatized biopsy site. The entire resected specimen was then opened, described, and fixed *in toto*, usually within 15 to 30 minutes after its removal. The earlier biopsies were fixed in Zenker-formol and formalin and the later ones in Bouin and formalin. In one case (Case 3) the gastric mucosa was exposed to the air for a period of 20 minutes while the specimen was being described. This produced alterations in the surface of the mucosa (Fig. 3b).

In describing the histologic findings of the original and post-resection biopsy specimens, the classification of gastritis presented by one of us¹ was employed.

A survey of the main features of each of these forms of gastritis is briefly presented.

1. Superficial Gastritis.—The stroma of the papilla is infiltrated by plasma cells, eosinophils, Russell bodies and lymphocytes in the chronic form, and

CLASSIFICATION OF GASTRITIS

- 1 Superficial—focal or diffuse
 - a Acute—with or without erosions
 - b Chronic—with or without erosions
- 2 Interstitial—focal or diffuse
 - a Acute
 - b Chronic.
- 3 Atrophic
 - a Productive and infiltrative—basal
 - 1 Focal
 - 2 Diffuse
 - b Infiltrative—with or without follicle formation
 - 1 Focal
 - 2 Diffuse.
 - c Metaplastic
 - 1 Focal
 - 2 Diffuse
 - d With focal hyperplasia of necks or pits and occasionally polyp formation

by polymorphonuclear leukocytes in the acute type. Edema of variable degree is present in both acute and chronic superficial gastritis, erosions may occur in either.

2 Interstitial Gastritis—The stroma between the necks of the gastric glands is infiltrated mainly by lymphocytes, which may form large aggregates or even follicles. In severe interstitial gastritis an increase in the collagenous fibers of the stroma occurs. Simultaneous atrophic changes in the neck portions of the glands result in distortion of the architecture of this region.

3 Atrophic Gastritis—The greatest atrophic changes and alterations are encountered in this type of gastritis. The increase in collagenous tissue of the stroma and smooth muscle fibers derived from the muscularis mucosae, usually accompanied by cellular infiltration, are always associated with an atrophic disappearance of glandular elements, whether focal or diffuse. These changes can be so extensive that the entire mucosa with the exception of the surface cells may be replaced by infiltrated collagenomuscular tissue (productive and infiltrative type) or lymphoid aggregates or follicles (infiltrative type) or both. In the latter, the production of tumorous masses or even pyloric obstruction (pseudohypertrophy) may be observed.

In the metaplastic form the surface epithelium, or that of any portion of the gastric glands, may be replaced by intestinal, goblet, and even Paneth cells. These features are associated with changes of the infiltrative, or productive and infiltrative type. The involved areas of the mucosa significantly altered and functionally atrophic may show papular or diffuse thickenings (pseudohypertrophy).

The histologic findings in the original and postresection biopsies are summarized in Table III. Five cases are recorded in detail.

TABLE III

Path No	Sex	Age in Years	Diagnosis	Interval in Minutes between Incision in Abdomen and			Site of Biopsies	Histologic Diagnosis Type of Gastritis**	
				Original Biopsy	Interval in Minutes between Original Biopsy and Removal of Resected Specimen	Interval in Minutes between Removal of Resected Specimen and Postresection Biopsy		Original Biopsy	Postresection Biopsy
68897 [†]	M	30	Chronic peptic ulcer of duodenum	3	27	5	Antrum	Superficial—acute and chronic Interstitial—acute and chronic Atrophic—basal moderate chronic infiltrative and productive. Focal metaplastic	Superficial—chronic Interstitial—acute and chronic Atrophic—basal moderate chronic infiltrative and productive
70148 [†]	M	23	Chronic peptic ulcer of duodenum	5	18	2	Antrum	Superficial—chronic Interstitial—acute and chronic Atrophic—mild basal chronic infiltrative and productive	Superficial—chronic Interstitial—acute and chronic Atrophic—mild basal chronic infiltrative and productive
70257	M	30	Chronic peptic ulcer of duodenum ^{††}	10	55	2	T Z #	Superficial—mild chronic Interstitial—focal subacute Atrophic—basal chronic infiltrative and productive	Superficial—chronic Interstitial—chronic Atrophic—basal chronic infiltrative and productive
70258 ⁺	M	52	Jejunal ulcer	10	17	2	Corpus at T Z	Corpus at T Z Superficial—Chronic Interstitial—chronic and focal acute Atrophic—basal moderate chronic infiltrative and productive	Corpus at T Z Superficial—chronic Interstitial—chronic and focal acute Atrophic—mild focal chronic basal infiltrative and productive
							Antrum	Antrum Superficial—chronic Interstitial—chronic with atrophy and mild acute Atrophic—basal chronic infiltrative and productive	Antrum Superficial—chronic Interstitial—chronic with atrophy Atrophic—basal chronic infiltrative and productive. Lymphoid follicles
70308*	M	51	Chronic peptic ulcer of stomach	30	10	5	Antrum	Superficial—chronic and focal acute Interstitial—chronic and focal acute Atrophic—basal chronic infiltrative and productive. Lymphoid follicles. Extensive metaplastic	Superficial—chronic and focal acute Interstitial—chronic and focal acute Atrophic—basal chronic infiltrative and productive. Lymphoid follicles. Moderately extensive metaplastic

HISTOLOGY FOLLOWING GASTRECTOMY

TABLE III (Continued)

70343 [†]	M	23	Chronic peptic ulcer of duodenum	8	40	1	Antrum	Superficial—chronic Interstitial—chronic and focal acute Atrophic—basal subacute and chronic infiltrative and productive	Superficial—chronic and focal acute with micro- scopic erosions † Interstitial—chronic and focal acute Atrophic—basal subacute and chronic infiltrative and productive Lym- phoid follicles Small focus of acute
70421*	F	56	Chronic N R peptic ulcer of duodenum ^{†*}	25		5	Antrum	Superficial—chronic Interstitial—chronic Atrophic—basal chronic infiltrative and produc- tive Focal acute	Superficial—chronic and focal acute Interstitial—chronic and scattered focal acute Atrophic—basal chronic infiltrative and produc- tive Lymphoid folli- cles Focal acute
70457*	M	54	Chronic peptic ulcer of duodenum	2	35	10	Antrum	Superficial—chronic Interstitial—chronic and acute Atrophic—basal subacute and chronic infiltrative and productive Lym- phoid follicles	Superficial—chronic Interstitial—chronic and mild subacute Atrophic—basal subacute and chronic infiltrative and productive Lym- phoid follicles and ag- gregates
70584*	M	43	Peptic ulcer of duodenum in healed stage	15	32	1	Corpus near T Z	Superficial—chronic Interstitial—mild chronic and focal acute Atrophic — basal mild chronic infiltrative and productive	Superficial—chronic Interstitial—mild chronic Atrophic—basal mild and focal moderate chronic infiltrative and produc- tive Focal lymphoid aggregates
70771*	M	28	Chronic peptic duo- denal ulcer (at line of resection) Healing erosion of duodenum proximal to ulcer	3	N R	5	Antrum	Superficial—chronic Interstitial—chronic and acute Atrophic—basal moder- ate chronic infiltrative and productive Lymphoid aggregates and follicles (Com- plete replacement of glands to necks in some foci)	Superficial—chronic Interstitial—chronic and focal acute Atrophic—basal chronic infiltrative and pro- ductive Lymphoid aggregates and folli- cles
70971*	M	43	Ulcerated infiltrating scirrhous adeno- carcinoma of stomach with lymph node in- volvement	7	N R	4	Corpus near T Z	Superficial—mild chronic Interstitial—mild chronic and focal acute. Atrophic — basal mild chronic infiltrative and productive Focal wedges of severe in- volvement Small lymphoid aggregates	Superficial—mild chronic Interstitial—mild chronic and focal severe chron- ic Focal acute Atrophic—basal chronic infiltrative and pro- ductive Focal wedges of severe involvement Small lymphoid aggre- gates
71341*	M	50	Healed peptic ulcer of duodenum **	10	30	2	T Z	Superficial — mild and focal moderate chronic Interstitial — mild and focal severe chronic Atrophic — basal mild chronic infiltrative and productive, focally more severe	Superficial—mild chronic Interstitial — mild and focal severe chronic Atrophic — basal focal moderate chronic infil- trative and productive

TABLE III (Continued)

71476*	I	53	Healed ulceration of anterior wall of first portion of duodenum with stenosis	5	23	2	T Z	T Z	T Z
								Superficial — moderate chronic	Superficial — moderate chronic
								Interstitial — moderate chronic and acute	Interstitial — mild to moderate chronic
								Atrophic—basal moderate chronic and subacute infiltrative and productive	Atrophic—basal moderate chronic infiltrative and productive
						Antrum	Antrum		Antrum
								Superficial—moderate to severe chronic	Superficial—moderate to severe chronic Focal metaplasia of surface cells and pits
								Interstitial — severe chronic and acute Metaplastic necks	Interstitial — severe chronic and moderate acute Metaplastic necks
								Atrophic—basal severe chronic infiltrative and productive Lymphoid aggregates and follicles	Atrophic — basal severe chronic infiltrative and productive Lymphoid aggregates and follicles Focal metaplastic
72820	M	61	Penetrating peptic gastric ulcer on lesser curvature ¹⁴ Healed peptic ulcer of first portion of duodenum ¹¹	10	40	2	Antrum	Superficial — moderate chronic	Superficial—chronic
								Interstitial—chronic and focal acute	Interstitial—chronic and focal acute
								Atrophic—basal chronic infiltrative and productive Lymphoid aggregates	Atrophic—basal chronic infiltrative and productive Lymphoid aggregates and a few follicles
73439	M	51	Scar of healed peptic ulcer of duodenum ¹¹	5	25	2	Antrum	Superficial—chronic	Superficial—chronic
								Interstitial—chronic	Interstitial—chronic and mild focal acute
								Atrophic—basal moderate chronic infiltrative and productive Lymphoid follicles	Atrophic — basal mild chronic infiltrative and productive Lymphoid follicles
74109	M	41	Chronic penetrating and perforating peptic ulcer of duodenum ¹¹	20	58	2	Antrum at T Z	Superficial—chronic	Superficial—chronic
								Interstitial—chronic with atrophic change	Interstitial—chronic with atrophic change
								Atrophic—basal chronic infiltrative and some productive Lymphoid aggregates and follicles	Atrophic—basal chronic infiltrative and productive Lymphoid aggregates and follicles
74121	M	49	Penetrating peptic ulcer of esophagus**	5	30	2	Corpus near T Z	Superficial—chronic	Superficial—chronic
								Interstitial—focal chronic	Interstitial—focal chronic
								Atrophic—basal chronic infiltrative and productive Focal lymphoid follicles	Atrophic—basal mild focal chronic infiltrative and productive Lymphoid aggregates and follicles
74502	M	60	Chronic peptic ulcer of duodenum Old gastro enterostomy	10	30	2	T Z at antrum	Superficial—chronic	Superficial—chronic
								Interstitial—mild chronic with mild atrophy	Interstitial — mild to moderate chronic
								Focal severe chronic	Atrophic—basal mild to moderate chronic infiltrative and productive Focal metaplastic
								Atrophic—basal moderate chronic infiltrative and productive Lymphoid aggregates	

HISTOLOGY FOLLOWING GASTRECTOMY

TABLE III (Continued)

74659	M	41	Scar tissue involving duodenum just beyond pylorus with resultant stenosis *†	6	24	35	T Z near antrum	Superficial—mild to moderate chronic Interstitial—mild to moderate chronic with atrophy Atrophic—basal moderate chronic infiltrative and productive Focal acute inflammation of muscularis mucosae	Superficial—mild to moderate chronic Interstitial—mild to focal severe chronic Atrophic—basal mild to moderate chronic infiltrative and productive Lymphoid aggregates
74795	F	52	Chronic peptic ulcer of duodenum Pyloric stenosis	15	45	1	Antrum	Superficial — moderate chronic Interstitial—mild acute and moderately severe chronic Atrophic—basal moderately severe chronic infiltrative and productive Lymphoid aggregates and small follicles	Superficial — moderate chronic Interstitial—mild acute and moderately severe chronic Lymphoid follicles Atrophic—basal moderately severe chronic infiltrative and productive Lymphoid aggregates and small follicles
75170	M	43	Scar of healed peptic ulcer of first portion of duodenum ††	3	16	2	Antrum	Superficial — moderate chronic Interstitial — moderate chronic and mild acute Atrophic—basal moderate chronic infiltrative and productive Basal mild acute Focal metaplastic Lymphoid follicles	Superficial — moderate chronic Interstitial — moderate chronic and acute Focal atrophy Atrophic—basal moderate chronic infiltrative and productive Basal mild acute Focal metaplastic Lymphoid follicles
75213	M	47	Penetrating peptic ulcer of duodenum ††	2	23	5	T Z	Superficial—mild to moderate chronic Interstitial—focal moderate chronic Atrophic — basal focal mild chronic infiltrative and productive Small lymphoid follicles	Superficial—mild to moderate chronic Interstitial—focal moderate chronic Atrophic — basal focal mild chronic infiltrative and productive Small lymphoid aggregates
75330	M	46	Penetrating peptic ulcer of duodenum	11	16	2	Antrum	Superficial — severe chronic Interstitial — severe chronic Atrophic — basal severe chronic infiltrative and productive Large lymphoid follicles with focal complete replacement of mucosa	Superficial — severe chronic Interstitial — severe chronic Atrophic — basal severe chronic infiltrative and productive Extensive infiltration with lymphoid follicles and focal complete replacement of mucosa
75642	M	49	Chronic peptic ulcer of duodenum	7	N R	3	T Z	Superficial—mild to moderate chronic Interstitial—focal mild and one focus of severe chronic Atrophic — basal focal mild to severe chronic infiltrative and productive Small lymphoid aggregate	Superficial — mild chronic Interstitial—mild focal chronic Atrophic — basal focal mild to moderate chronic infiltrative and productive Small lymphoid aggregate

TABLE III (Continued)

75918	M	50	Puckered stellate scar of anterior wall of duodenum 1†	14	25	15	T Z	Superficial—mild chronic Interstitial — mild and focal moderate chronic Atrophic — basal focal mild chronic infiltrative and productive Focal lymphoid aggregate	Superficial — mild to moderate chronic Interstitial — mild to moderate chronic Atrophic—basal mild to moderate chronic productive and infiltrative Large lymphoid aggregate
76542	M	40	Scars in anterior and posterior walls of first portion of duodenum 4†	5	28	2	Corpus near T Z	Superficial—mild chronic Interstitial — moderate and focal severe chronic with focal atrophic change Atrophic—basal mild and focal moderate chronic infiltrative and productive Lymphoid follicles	Superficial—mild chronic Interstitial — moderate and focal severe chronic with focal atrophic change Atrophic—basal mild and moderate chronic infiltrative and productive Lymphoid follicles
76566	M	53	Chronic peptic ulcer of duodenum	4	16	1	Corpus near T Z	Superficial — focal mild chronic Interstitial — mild to moderate and focal severe chronic with atrophic change Atrophic—basal mild to moderate and focal severe chronic infiltrative and productive Lymphoid aggregates and follicles	Superficial — focal mild chronic Interstitial — mild to moderate and focal severe chronic with atrophic change Atrophic—basal mild to moderate and focal severe chronic infiltrative and productive Lymphoid aggregates and follicles
76588	M	65	Scar in superior wall of 1st portion of duodenum **	5	16	1	Antrum	Superficial—chronic Interstitial—chronic with atrophic change and lymphoid follicles Atrophic—basal moderate and focal severe chronic infiltrative and productive Lymphoid aggregates and occasional follicle	Superficial—chronic Interstitial—chronic with atrophic change and lymphoid follicles Atrophic—basal moderate and focal severe chronic infiltrative and productive Lymphoid aggregates and occasional follicle
76778	M	41	Healed peptic ulcer of anterior wall of 2nd portion of duodenum Penetrating jejunal ulcer **	5	50	3	Corpus near T Z	Superficial — moderate chronic Interstitial—chronic and focal acute Atrophic — basal mild chronic focal infiltrative and productive	Superficial — moderate chronic Interstitial—chronic and focal acute Atrophic — basal mild chronic focal infiltrative and productive
76831	M	57	Perforating peptic ulcer of pylorus **	5	23	6	Antrum	Superficial—chronic Interstitial—chronic with atrophic change Focal metaplastic Atrophic—basal moderately severe chronic infiltrative and productive Lymphoid aggregates and follicles	Superficial—chronic Interstitial—chronic with atrophic change Focal metaplastic Atrophic—basal moderately severe chronic infiltrative and productive Lymphoid aggregates and follicles

HISTOLOGY FOLLOWING GASTRECTOMY

TABLE III (Continued)

76865	M	53	Ulcerated infiltrating scirrhous adeno- carcinoma of stomach with in- volvement of lymph nodes	2	31	2	Corpus at T Z	Superficial—none Interstitial—none Atrophic — basal focal chronic infiltrative and productive	Superficial—none Interstitial—small focus of moderate chronic Atrophic — basal focal chronic infiltrative and productive
76950	M	51	Chronic peptic ulcer of jejunum	35	55	2	T Z	Superficial—mild to mod- erate chronic Interstitial—focal mod- erate chronic Atrophic—focal moderate basal chronic infiltra- tive and productive Lymphoid aggregates Focal extensive meta- plastic with polymor- phonuclear leukocytic infiltration and lymph- oid aggregates and follicles	Superficial—mild to mod- erate chronic Interstitial—focal mod- erate chronic Atrophic — moderate basal chronic infiltra- tive and productive More lymphoid aggre- gates Focal meta- plastic
77039	M	38	Several scars of anterior wall of pylorus **	7	15	1	Antrum	Superficial — moderate chronic Interstitial — severe chronic Atrophic — severe basal chronic infiltrative with lymphoid follicles and moderate productive	Superficial — moderate chronic Interstitial — severe chronic Atrophic — severe basal chronic infiltrative with lymphoid follicles and moderate productive
77098	M	32	Scar of anterior duodenal wall with slight con- striction of second portion of duodenum *†	5	12	2	T Z	Superficial—mild chronic Interstitial—focal acute and chronic Atrophic — mild basal chronic infiltrative and productive Lymphoid aggregates	Superficial—mild chronic Interstitial—focal acute and chronic Atrophic — mild basal chronic infiltrative and productive Lymphoid aggregates
77411	M	48	Peptic ulcer of anterior wall of duodenum Scars of superior duodenal wall just beyond pylorus ** Duodenal erosion in healing state	10	5	10	Antrum	Superficial—chronic Interstitial—chronic with atrophy and focal acute Atrophic — severe basal chronic infiltrative and productive Lymphoid aggregates and follicles	Superficial—chronic Interstitial—chronic with atrophy and focal acute Atrophic — severe basal chronic infiltrative and productive Lymphoid aggregates and follicles

Meaning of notations on table.

* Indicates the utilization of a rubber covered intestinal clamp to obtain the original biopsy

** Designates the surgical diagnosis in those cases in which the ulcer was left *in situ*. All the others are pathologic diagnoses

Case 1—Path No 70308 Male, age 51, admitted in April, 1940 Three years before admission the patient had epigastric pain at irregular intervals after meals for a period of three months A gastro-intestinal series, taken in 1937, demonstrated a moderately large ulcer involving the lesser curvature and posterior wall of the stomach During the past four months there was increasingly severe epigastric pain and occasional vomiting Roentgenograms demonstrated that the ulcer previously noted had diminished considerably in size Wassermann—negative Rehfuß' test meal—maximum free acid 30, maximum total acid 54 Night Rehfuß'—free acid 0, maximum total acid 32 Vagus test meal—maximum free acid 60, maximum total acid 82

The patient was prepared with parenteral 5% glucose in physiologic saline Prior to operation cevitic acid, yeast tablets, vitamin B complex and nicotinic acid were administered by mouth, and seconal gr 3 by rectum Immediately before anesthesia, magendie minims 6 and atropine gr 1/150 were given hypodermically

Operation was performed, April 11, 1940, under cyclopropane anesthesia The stomach was found to be slightly dilated In the region of the coronary artery there was an indurated area which measured approximately four centimeters in diameter This lesion presented a definite crater The ulcer penetrated posteriorly and was sealed off by adherent jejunum which had found its way into the lesser sac

The original biopsy was taken 30 minutes after incision of the abdomen, from the anterior wall of the stomach in the antral region two centimeters cephalad to the greater curvature The resected specimen was removed ten minutes later The post-resection biopsy was taken from the edges of the original biopsy wound five minutes after removal of the specimen Both biopsies were cut into strips approximately one millimeter in width and fixed at once in Zenker-formol and formalin

HISTOLOGY OF THE BIOPSIES—*Original Biopsy—Antrum* (See Fig 1a) The formalin-fixed tissue consists of four strips, two of which measure 1.5 cm in length, a third which measures 1 cm in length, and a fourth which measures 0.7 cm in length The Zenker-formol-fixed tissue consists of two pieces which measure 1.5 and 2 cm in length, respectively

The architecture of the mucosa is considerably altered The surface, even on gross inspection, is irregularly nodular The nodules are separated by depressed, widened deeper pits In a few areas, the glandular elements have been replaced by moderately cellular, very loose, edematous fibrous tissue infiltrated by plasma cells, a moderate number of eosinophils and a small number of polymorphonuclear leukocytes Acini of neck and antral glands are scattered within this tissue In the deeper third of the mucosa there is loose connective tissue of finely fibrillar character that contains numerous single muscle fibers and bundles of muscle fibers continuous with the muscularis mucosae and infiltrated by lymphocytes, plasma cells and a moderate number of eosinophils Small lymphoid aggregates and lymphoid follicles surrounded by denser collagenous tissue and muscle bundles are present In the neighborhood of some of these follicles there are antral glands of more regular appearance, with flattened basal nuclei These portions of the mucosa occur between the depressed pits and are often wider than those occupied by the glandular elements

The gastric glands are replaced by glands of intestinal type in large portions of each of the biopsy strips These glands occupy only the superficial two-thirds or one-half of the mucosa They are lined by columnar or cuboidal cells with neutrophilic

*** Diffuse unless specifically noted to be focal

† The isolated observation of microscopic erosions in this case in an exquisitely focal disease like gastritis cannot be evaluated No active erosions were found in any of the other 34 cases of this series

Transitional zone of the gastric mucosa between that of the corpus and that of the antrum In this zone the peptic glands occupy a narrow portion of the mucosa just above the muscularis mucosae and antral glands often containing acid cells larger portions of the mucosa In the antral region the antral glands extend to the muscularis mucosae

Interval not recorded

HISTOLOGY FOLLOWING GASTRECTOMY

or basophilic cytoplasm and brush borders. Goblet cells occur amongst them. Many of the nuclei are pseudostriated. They vary considerably in size, shape and staining intensity. A few of the nuclei are very large, with finely granular chromatin and large eosinophilic nucleoli. There are more mitoses among the intestinal cells than among the remnants of degenerating gastric glands. Around the intestinal glands there is loose moderately cellular fibrous tissue infiltrated by plasma cells, a moderate number of eosinophils and a few polymorphonuclear leukocytes.

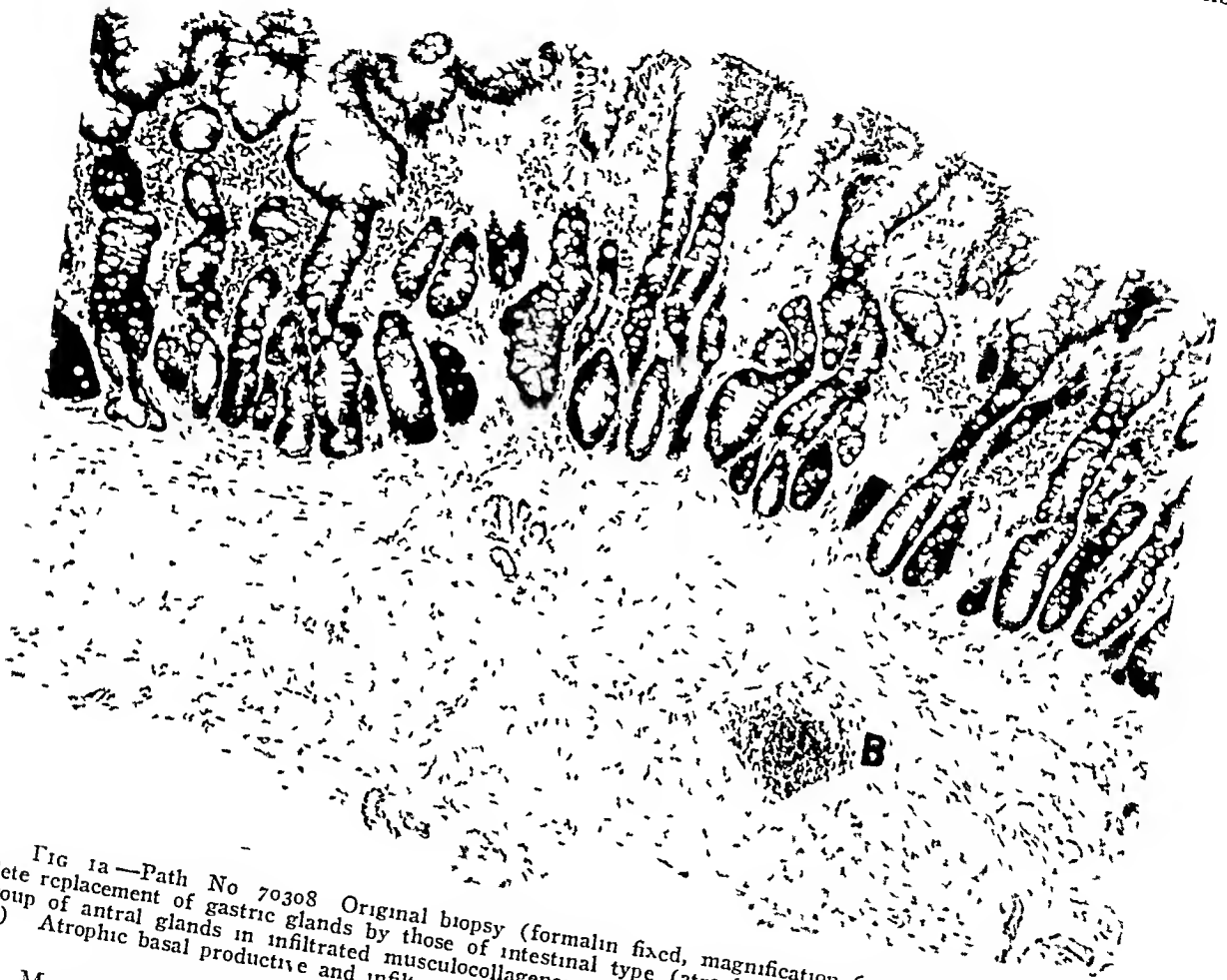


FIG 1a—Path No 70308 Original biopsy (formalin fixed, magnification 62 times) Note complete replacement of gastric glands by those of intestinal type (atrophic metaplastic gastritis). Small group of antral glands in infiltrated musculocollagenous tissue (a) Small basal lymphoid aggregate (b) Atrophic basal productive and infiltrative gastritis. The width of the mucosa is unchanged.

Most of the mucosal surface is lined by cells which are of intestinal type. Pseudo-stratification, which produces the appearance of budding, is present in many areas. The nuclei are elevated to the free borders of the cells. Focally, the surface lining cells are markedly flattened, widened and distorted, with vacuolated cytoplasm and pyknotic nuclei. Polymorphonuclear leukocytes, an occasional eosinophile and some lymphocytes are present in or between these cells. In a few areas the surface lining cells contain atypical nuclei which are large, swollen, hyperchromatic, and bound by poorly outlined nuclear membranes. The basement membranes beneath the cells of intestinal type vary in their demarcation. Thin mucus, in which a few desquamated epithelial cells, a small number of polymorphonuclear leukocytes and some red blood cells are found, covers the surface of the mucosa.

The papillae vary in shape, many are edematous. Some are flat and wide, others are rounded and separated by the moderately wide lumina of glands lined by intestinal epithelium. In the Zenker-formal-fixed sections many contain fine, granular, eosinophilic material (fixed edema fluid). In a moderate number the eosinophilic material is very

dense and forms a homogenous laver between the capillaries and the basement membranes of the surface lining cells. The papillae are infiltrated by many plasma cells, some contain extravasated red blood cells.

In the portions of the mucosa replaced by collageno-muscular tissue, and deep to the intestinal glands, there are remnants of neck glands and antral acini. These are of degenerative character. In many of the cells no mucus is present along the free border. The nuclei are irregularly arranged and vary in size, shape and staining intensity. The basement membranes around the acini are barely visible or absent. Some

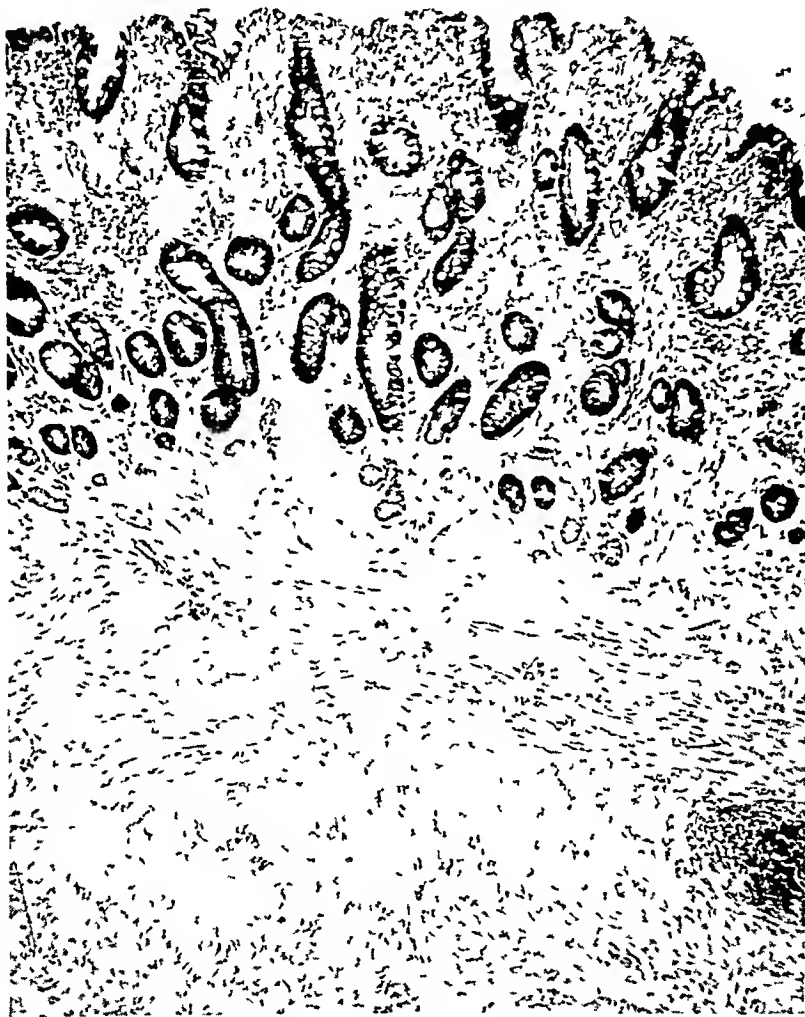


FIG 1b—Path No 70308 Post resection biopsy (formalin fixed, magnification 62 times). The features are essentially similar to those described in Figure 1a. The surface cells in this area are slightly more distorted.

of the acini are dilated, and lined by narrow layers of cytoplasm. Scattered mitoses and a moderate number of argentaffine cells are present among these degenerating glandular acini. In the Zenker-formol-fixed section more gastric neck glands and antral glands are present. Russell bodies are found among the infiltrating cells in these regions. The junction of the muscularis mucosae with the mucosa is not clear in many places due to the proliferation of muscle fibers that extend into the upper half of the mucosa. Edema is evident throughout the mucosa but is most prominent in the papillae and just above the muscularis mucosae.

Capillaries are present within the superficial $\frac{1}{2}$ to $\frac{1}{4}$ of the mucosa. These are of uneven caliber and measure from one to eight erythrocytes in diameter. The infiltrated musculo-collagenous tissue contains scattered venules of larger caliber which are so widely spaced that the mucosa appears relatively avascular. In the deeper portions of the mucosa there are capillaries filled with eosinophilic granular material and a few dilated lymphatic channels. The walls of the capillaries both here and in the papillae are not clear.

In the Zenker-formol-fixed sections the lymphoid aggregates and small follicles are more numerous than in those fixed in formalin. From these basal foci the muscularis



FIG 1c—Path No 70308 Post resection biopsy (Zenker-formol fixed, magnification 62 times). Note the extensive mucosal hemorrhage. Character of the mucosa is otherwise similar to that of Figures 1a and 1b. Note the unchanged surface cells and glands.

mucosae is infiltrated by lymphocytes. In one place the lymphoid aggregates extend through the muscularis mucosae into the submucosa and focally replace the muscle fibers. The muscularis mucosae itself is edematous. The submucosa consists of loose connective tissue with dilated congested veins and arteries. Just beneath the muscularis mucosae there are some large dilated lymphatic channels. A few small islands of fat cells are present.

The septa of the muscularis propria contain extravasated red blood cells and foci of hemorrhage. The muscle cells are without significant change. The serosa contains congested capillaries and is slightly edematous.

Postresection Biopsy—Antrum (See Fig 1b). The formalin-fixed specimen consists of one strip, which measures 1 cm in length. The Zenker-formol-fixed specimen consists of three strips, each of which measures 1 cm in length.

The fundamental architecture of the mucosa is similar to that of the original biopsy. The surface is slightly less nodular. It is covered by mucus of slightly denser character that contains more polymorphonuclear leukocytes, some lymphocytes, and more erythrocytes.

The edema of the papillae, the congestion of the capillaries and venules in the superficial portions of the mucosa and the extravasation of erythrocytes are greater

than in the original biopsy sections. Above the muscularis mucosae the edema is slightly less intense.

One of the strips taken from the very edge of the original biopsy wound (see Fig 1c) presents extensive hemorrhage into the mucosa. It is interesting to note that even here no greater changes are found in the surface lining cells than in the original biopsy specimens. The shape of the papillae is unaltered by the recent hemorrhage. The infiltrating cells are separated by the erythrocytes and appear less numerous, but the type of gastritis is similar.

Above the muscularis mucosae the congestion of the vessels is but slightly more prominent.

The submucosa is more edematous. Its vessels are more congested. Foci of extensive hemorrhage are present. Scattered through the submucosa are a few dilated lymphatic channels. The lumina of the dilated veins contain erythrocytes centrally, and polymorphonuclear leukocytes and some eosinophils along the endothelial lining of their walls. The septa of the muscularis propria and the serosa are without significant change.

Case 2—Path No 72820. Male, age 61, was admitted to the hospital in November, 1940. He complained of aching intermittent epigastric pain of one and one-half years duration. The pain lasted for one to two hours, occurred irregularly, and subsided without treatment. During the past month the pain became more severe, lasted five to six hours, and was accompanied by anorexia and occasional vomiting. He had lost six pounds in weight and complained of increasing weakness. Wassermann—negative. Rehfuess' test meal—maximum free acid 65, maximum total acid 90. Night Rehfuess'—maximum free acid 34, maximum total acid 54. Vagus test meal—maximum free acid 60, maximum total acid 74.

The patient was prepared for operation with parenteral 5% glucose in physiologic saline. Magendie minims 6 and atropine gr 1/150 were given hypodermically prior to anesthesia.

Operation was performed, November 14, 1940, under cyclopropane and ether anesthesia. The stomach was found to be slightly dilated. Scar tissue surrounded the first portion of the duodenum due to previous ulceration. Posteriorly, high on the lesser curvature near the esophagus, there was a penetrating ulcer whose base was formed by the pancreas. The lesion was surrounded by edema that extended to the recentrant angle. No enlarged lymph nodes were present. The ulcer was not removed inasmuch as a Madelener procedure was performed.

The original biopsy was taken ten minutes after incision of the abdomen, from the anterior wall of the stomach in the antral region approximately two centimeters cephalad to the greater curvature. The resected specimen was removed 40 minutes later. Two minutes after its removal the post-resection biopsies were obtained from the edges of the original biopsy wound. Both biopsies were cut into narrow strips approximately one millimeter in width, and placed in Bouin and formalin immediately.

HISTOLOGY OF THE BIOPSIES—*Original Biopsy*—*Antrum* (see Fig 2a). The formalin specimen consists of two strips, each of which measures approximately 1.3 cm in length, the Bouin specimen consists of two strips, each of which measures 1 cm in length.

The architecture of the mucosa is moderately distorted in the neck region and more distorted in the basal portions of the mucosa occupied by the antral glands. These alterations are greater in the formalin-fixed specimens than in those fixed in Bouin. The surface of the mucosa in all the specimens is relatively flat except where the markings of the gastric areas are faintly discernible. Small, narrow linear fragments of mucus that contain a few polymorphonuclear leukocytes are scattered over the surface.

The surface lining cells over many of the papillae are relatively unchanged. Their nuclei are oval and occupy their usual position in the cell slightly above the base. Over some of the papillae, however, the surface cells show basal vacuolization and eleva-

HISTOLOGY FOLLOWING GASTRECTOMY

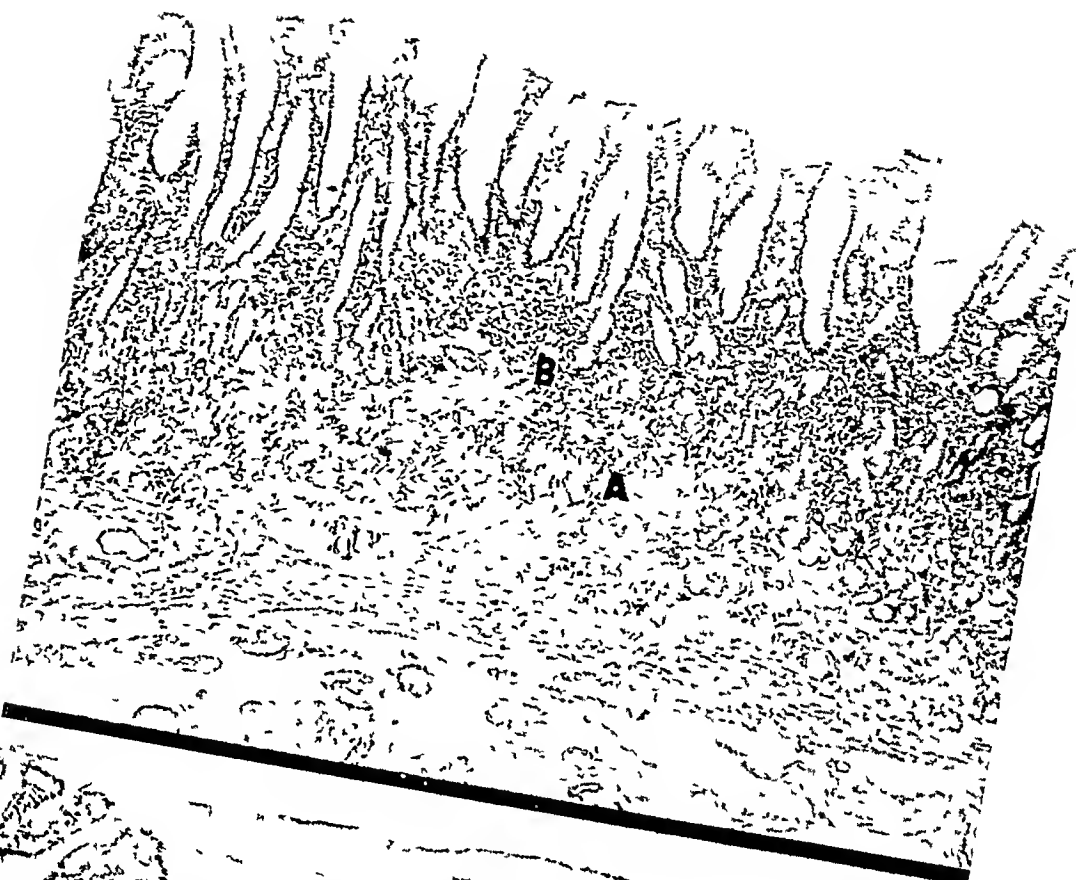


FIG 27—Path No 72820 Original biopsy (Bouin fixed, magnification 62 times)
Note the marked distortion of architecture and the bundles of muscle fibers Islands
of intral gland acini (A) Horizontal neck gland acini (B)
FIG 28—Path No 72820 Post resection biopsy (Bouin fixed, magnification 62
times) Note the edema of the papillae and the thick layer of mucus over the surface
The other features are essentially similar to those described in Figure 27

tion of the nuclei which are irregular in shape, position and staining intensity. The papillae contain a moderate number of plasma cells. Edema of the papillae varies so that some are wide and flat and others are pointed.

Some of the pits are slightly dilated and contain polymorphonuclear leukocytes, others are of average caliber. The neck glands are separated by stroma that is infiltrated with plasma cells, scattered eosinophils and some polymorphonuclear leukocytes. Around some of the necks small foci of polymorphonuclear leukocytes may be seen. Muscle bundles parallel to the surface of the mucosa penetrate to the pit-neck junctions, and form moderately large groups of fibers in some areas. The long axes of most of the neck glands are perpendicular to the surface of the mucosa, some are oblique. The basement membranes of many of the neck gland acini are no longer discernible. The lumina of some of the acini are dilated and contain polymorphonuclear leukocytes. The acini present a moderate number of mitoses and contain argentaffine cells. In some areas the neck gland acini are but shrunken remnants.

The antral glands in the basal half of the mucosa are decreased in number. They are replaced by bundles of smooth muscle fibers and by a smaller amount of collagenous tissue of finely fibrillar character. At some points continuity of the muscle bundles in the mucosa with the muscle fibers of the muscularis mucosae is evident. The fine fibrillar collagenous tissue is infiltrated by lymphocytes, occasional eosinophils and a few polymorphonuclear leukocytes. The groups of muscle fibers and the infiltrated collagenous tissue separate the antral glands from the muscularis mucosae and isolate small groups of antral acini. This produces the appearance of islands of acini in the altered stroma.

The antral gland acini are dilated, with many cells basally or superficially vacuolated. Their nuclei are irregular and vary considerably in character. These cellular changes occur in the islands of acini as well as in the closely approximated acini which lie in relatively unchanged stroma. In the latter areas, however, the nuclei are of more regular character. In the more dilated acini the lining cells are markedly flattened and contain but little or no mucus. Their nuclei are black, shrunken dots.

The portion of mucosa just above the muscularis mucosae contains lymphoid aggregates that extend into the muscularis mucosae at some points. In a few areas the lymphoid aggregates lie mainly within the muscularis mucosae. The muscle bundles of the latter are separated by edematous finely fibrillar tissue that is infiltrated by a moderate number of lymphocytes.

The capillaries of the papillae are congested and in places dilated. The walls of some of them are distinct, those of others merge with the basement membranes of the surface cells. The capillaries are of uneven caliber and are more dilated at the summits of the papillae than along the sides of the pits. These vessels range from one to two erythrocytes in width. There is a remarkable absence of visible vessels beneath the pit-neck junctions. Basally, above the muscularis mucosae dilated empty capillaries and venules are present.

The tissue of the submucosa is loose, somewhat edematous and contains moderately dilated, congested arteries and veins. Some of these vessels are filled with red blood cells and others with granular eosinophilic material. In the Bouin-fixed sections there are dilated lymphatic channels and small focal extravasations of erythrocytes.

The septa of the muscularis propria are slightly edematous. Around some of the nerves there is lymphocytic infiltration. An occasional eosinophile and lymphocyte is present around the venules of the septa. The serosa contains a few dilated congested venules and capillaries.

Postresection Biopsy—Antrium (see Fig. 2b). The formalin-fixed specimen consists of two pieces which measure 1.5 and 1.6 cm, respectively. The Bouin-fixed specimen consists of two pieces which measure 0.9 and 1 cm, respectively.

The microscopic architecture of the mucosa and its surface markings correspond to

those of the original biopsy The surface of the mucosa is covered by a wider layer of denser mucus that contains numerous erythrocytes and small clumps of polymorphonuclear leukocytes The entire mucosa is more edematous than that of the original biopsy The edema is better seen in the Bouin-fixed, than in the formalin-fixed tissue More of the surface cells show basal vacuolization than those of the original biopsy However, even over areas of marked edema of the papillae, the vacuolization of the individual cells is not greater The other changes of the surface cells, of the neck glands, and of the antral glands described in the original biopsy are seen here The infiltrating cells are similar in their distribution and number

The capillaries of the papillae are more congested but of somewhat narrower caliber Most of them are but one erythrocyte in width The changes in their walls are similar to those already noted in the original biopsy Above the muscularis mucosae the degree of vascular congestion is similar to that of the original biopsy except for an occasional dilated congested vein that penetrates the muscularis mucosae from the submucosa

The most marked differences in the gastric wall are seen in the submucosa There is extensive edema and hemorrhage near the edges of the original biopsy wound The arteries and veins are considerably dilated and congested The walls of the veins are infiltrated by polymorphonuclear leukocytes At a distance from the edges of the original biopsy the hemorrhage is focal and the edema is less prominent, but the congestion and dilatation of the vessels is similar Erythrocytes extend into the septa of the muscularis propria from the areas of extensive hemorrhage in the submucosa The capillaries of the muscularis propria, especially those near the serosa, are congested and surrounded by small foci of hemorrhage Many of the capillaries and small venules are filled with polymorphonuclear leukocytes that infiltrate their walls and extend into the adjacent fibrous tissue and muscle fibers The serosa is similar to that of the original biopsy sections

Case 3—Path No 74659 Male, age 41, entered the hospital in April, 1941 The patient was well until three years ago when he had one unheralded hematemesis Since then he experienced epigastric pains and belching For the past four months he complained of right upper quadrant pain and vomiting Two months ago he had had melena Two days prior to admission he suffered severe cramp-like pains accompanied by vomiting Wassermann—negative Rehfuß' test meal—maximum free acid 50, maximum total acid 70 Night Rehfuß'—maximum free acid 44, maximum total acid 52

The patient was prepared for operation with parenteral 5% glucose in physiologic saline Immediately before anesthesia, magendie minims 6 and atropine gr 1/150 were given hypodermically

Operation—April 21, 1941 Under spinal anesthesia, with 12 cc of Jones solution supplemented with ethylene and ether The stomach was dilated to two and one-half times its usual size There was increased vascularity Scar tissue which surrounded the duodenum immediately beyond the pylorus narrowed it to a diameter of one-half inch

The original biopsy specimen was taken six minutes after incision of the abdomen from the anterior wall of the stomach in the transitional zone near the antrum approximately two centimeters cephalad to the greater curvature of the stomach The resected specimen was removed 24 minutes later The original biopsy specimens were cut into strips approximately 1 mm in width and fixed in formalin and Bouin at once The entire specimen was then described with minimal manipulation Thirty-five minutes after its removal it was fixed in toto in Bouin solution Sections of the edges of the original biopsy wound were then taken from the fixed specimen

HISTOLOGY OF THE BIOPSIES—*Original Biopsy*—*Transitional Zone* (see Fig 3a) The formalin-fixed specimen consists of three strips that measure 0.5, 0.7 and 0.8 cm, respectively The Bouin specimen consists of two strips which measure 1.0 and 1.2 cm

The mucosal architecture is generally unchanged There is focal distortion in the

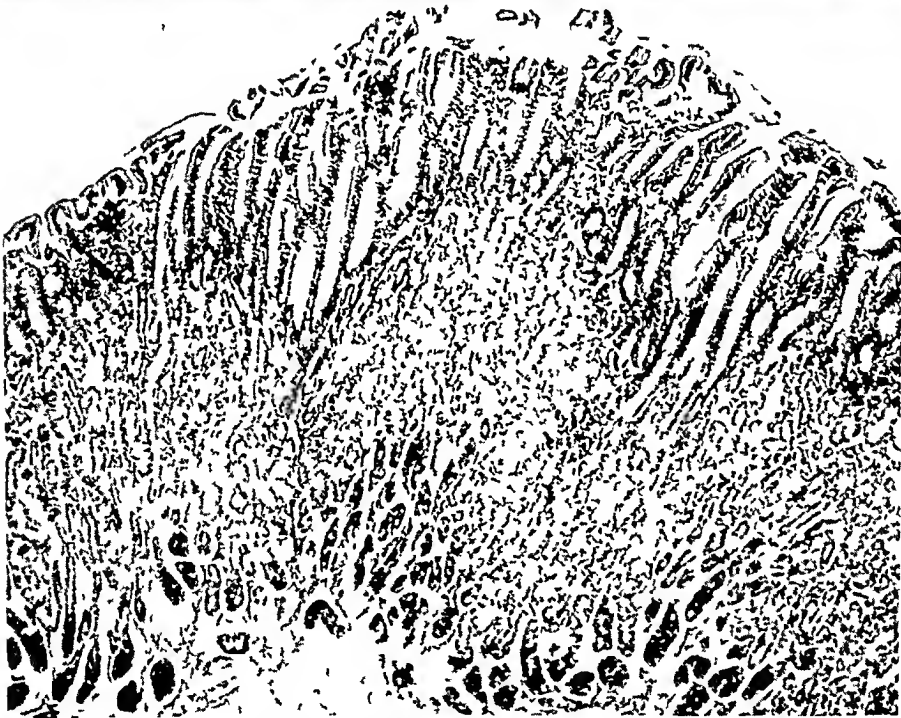
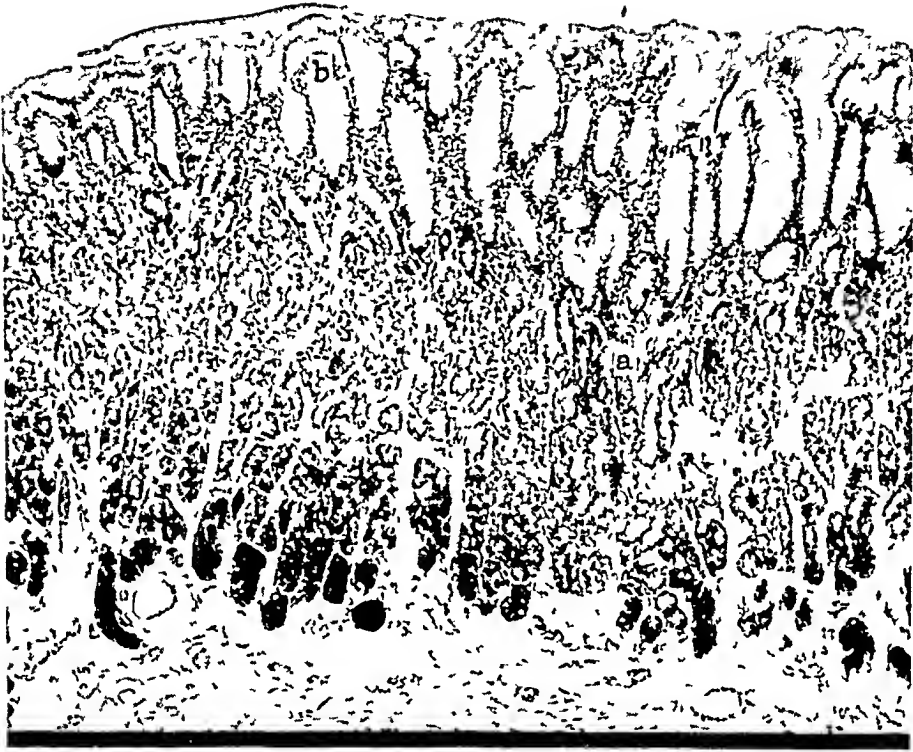


FIG 3a—Path No 74659 Original biopsy (Boun fixed, magnification 62 times) Note the separation of the surface cells from the papillae (artefact) The latter vary in width, height, and degree of infiltration Focal mild interstitial gastritis (a) The glands are elevated from the muscularis mucosae and separated from each other by edematous infiltrated, finely fibrillar, connective tissue Suprapapillary space filled with edema fluid (b)

FIG 3b—Path No 74659 Post resection biopsy (Boun fixed, magnification 52 times) Note the elongation of pits and necks, widening of the pits and focal villiform papillae produced by prolonged exposure to air before fixation Basal edema is slightly greater than in the original biopsy The summits of some of the papillae are torn (artefact) The other features are similar to those seen in Figure 3a

neck region and above the muscularis mucosae. The surface of the mucosa is flat. The gastric areas are not discernible. A thin layer of mucus that contains a few desquamated epithelial cells, an occasional polymorphonuclear leukocyte and erythrocytes covers portions of the mucosal surface and fills the pits.

The formalin-fixed tissue differs from that fixed in Bouin. In the former the majority of the surface cells contain the usual amount of mucus. Most of their nuclei are oval or round, some are concave superficially and irregular. The surface cells over a few of the papillae contain no mucus and are shorter than the cells adjacent to them. Their cytoplasm is basophilic. Some of the nuclei occupy almost the entire cell, whereas others are at the free border. Focal pseudostriatification is present in these areas. A moderate number of the cells, over both infiltrated and noninfiltrated papillae, are vacuolated basally. In the Bouin-fixed sections most of the surface cells are separated from the summits of the papillae by spaces. The major number of these spaces are empty, some contain eosinophilic granular material. The basal portions of many of the cells are no longer lined by basement membranes and are not clear. The nuclei, however, are not changed. In a few places the thin basement membranes are still visible beneath the cells. Here the basal changes in the cells are similar to those described in the formalin-fixed tissue.

The papillae vary in shape. Some are pointed, others are flat. Many are infiltrated by a moderate number of plasma cells, some lymphocytes and an occasional eosinophile or polymorphonuclear leukocyte. In these papillae there are more stromal nuclei. A small number of papillae contain extravasated red blood cells, others contain large amounts of eosinophilic, smooth material (fixed edema fluid). A few contain only edema fluid. In the Bouin-fixed sections the edema of the papillae is not as evident due to the expression of the serum into the spaces already noted between the surface cells and the summits of the papillae. The degree of infiltration is similar to that described in the formalin-fixed sections. The summits of the papillae beneath the spaces are covered by thickened, collagenous membranes of neutrophilic character.

The pits occupy one-fifth to one-quarter of the entire thickness of the mucosa. The neck glands are separated by edematous connective tissue infiltrated by small numbers of plasma cells, some lymphocytes and a few eosinophils. Their acini are surrounded by basement membranes. In a few areas no recognizable basement membranes are present. The neck cells of these acini are basally vacuolated, the acid cells are vacuolated, shrunken or deeply eosinophilic. There are small foci of denser lymphocytic infiltration between some of the neck acini. Amongst the lymphocytes a single degenerating deformed acinus is present, lined by irregular cells. In one such area the neck cells of the acinus are basophilic and granular. The cytoplasm approaches that of intestinal epithelium (dedifferentiation).

The glands in the middle third of the mucosa are separated by edematous, finely fibrillar connective tissue that contains a small number of plasma cells and lymphocytes. There is one small aggregate of lymphocytes between the glands at this level of the mucosa. The peptic glands in the basal portions of the mucosa are separated from the muscularis mucosae by edematous finely fibrillar, infiltrated connective tissue. At some points the peptic gland acini reach the muscularis mucosae. The glands nearest the muscularis mucosae contain peptic cells whose nuclei are near or at their free borders. The acid cells in these acini contain three to five nuclei, some of which are faintly stained and shrunken. The basement membranes of these acini may be thickened or absent. The cells of the latter merge with the edematous fibrillar connective tissue.

The mucosal glands in the formalin-fixed tissue are more closely approximated than in the Bouin-fixed specimens. This is due to less evident edema of the mucosa in the former sections.

The capillaries of the papillae in the Bouin-fixed sections are empty. They vary from one to three erythrocytes in width. At the pit-neck junctions there are venules

which vary from six to eight erythrocytes in width. Their walls are thickened. In the lower two-thirds of the mucosa there are scattered empty venules eight erythrocytes in width. Immediately above the muscularis mucosae there are dilated venules that contain eosinophilic granular material and erythrocytes. In the formalin-fixed sections the distribution of the vessels is more evident. Extravasation of red blood cells in the papillae and in small foci in the neck region are also more evident in these sections.

The demarcation of the mucosa from the muscularis mucosae is clear. The latter is edematous and contains a few lymphocytes and dilated venules which are empty or contain eosinophilic granular material. The arterioles within it are contracted. The submucosa in the Bouin-fixed tissue is edematous. The veins are dilated and contain eosinophilic granular material and some erythrocytes. The arterioles are contracted, the arteries are dilated and congested.

The septa of the muscularis propria are edematous and contain a small number of lymphocytes in some places. The serosa is moderately edematous.

Postsection Biopsy—Transitional Zone (see Fig 3b). The specimen consists only of Bouin-fixed tissue from the edges of the biopsy wound. One strip is 1.5 cm and the other 2.5 cm in length.

The mucosal architecture is essentially similar to that of the original biopsy. In some areas the pits are longer and the papillae elongated and narrower. Most of the pits are empty. The surface is flat. The gastric areas are not discernible. A thick layer of denser mucus that contains desquamated epithelial cells and masses of erythrocytes covers the surface. Among the erythrocytes there are strands of fibrin and in places many polymorphonuclear leukocytes. The amount of mucus in the surface cells over some of the papillae is less than in the original biopsy. Generally, however, the amount of intracellular mucus is similar.

The cellular infiltration of the papillae and of the stroma between the neck glands is focally greater than in the original biopsy. The edema of the upper two-thirds of the mucosa is less. Basally, however, in some areas the edema is greater. The pits, neck gland acini and peptic gland acini are essentially similar. The deepest of the peptic gland acini are often completely surrounded by edematous, finely fibrillar infiltrated, connective tissue.

The vascular distribution within the mucosa does not differ. Some of the venules near the muscularis mucosae contain polymorphonuclear leukocytes in their lumina and walls. These cells extend for a short distance into the surrounding tissue.

The muscularis mucosae is thinner. The infiltration within it and the edema are similar. The upper layers of the submucosa beneath the muscularis mucosae are occupied by large foci of hemorrhage. The veins and arteries are more dilated. They are congested and contain polymorphonuclear leukocytes which extend into the walls of some of the veins.

The septa of the muscularis propria adjacent to the submucosa are edematous. Some of the capillaries and venules within the septa contain polymorphonuclear leukocytes that extend into the walls of the vessels. Near the serosa the edema is less than in the original biopsy specimens. The serosa is less edematous.

Case 4—Path No 75213. Male, age 47, was admitted to the hospital in May 1941. He complained of sticking postprandial epigastric pain penetrating to the back and occasional tarry stools for the past ten months. A gastro-intestinal series demonstrated a duodenal ulcer. This responded to medical therapy until two months ago when the pain became intractable. Wassermann negative. Rehfuess' test meal—maximum free acid 40, maximum total acid 60.

The patient was prepared for operation with parenteral 5% glucose in physiologic saline. Magendie minims 6 and atropine gr 1/150 were given hypodermically before anesthesia.

Operation—June 5, 1941 Under spinal anesthesia, with 12 cc of Jones solution, supplemented by intravenous sodium pentothal. The stomach was found to be of normal size. Distal to the pylorus there was a mass of indurated tissue that pushed the duodenum to the left. A penetrating ulcer sealed by omentum occupied the superior portion of the duodenum. A resection with post-pyloric "auschaltung" was performed.

The original biopsy was taken two minutes after incision of the abdomen, from the anterior wall of the stomach in the transitional zone near the antrum, approximately two centimeters cephalad to the greater curvature. The resected specimen was removed 23 minutes later. Sections were taken from the edges of the original biopsy wound five minutes after removal of the stomach. Both biopsies were cut into strips, approximately one millimeter in width, and placed in Bouin and formalin immediately.

HISTOLOGY OF THE BIOPSIES—Original Biopsy—Transitional Zone (see Fig. 4a) The formalin specimen consists of three strips which measure 0.8, 0.7, and 1 cm, respectively. The Bouin specimen consists of three strips which measure 1.1, 1.2 and 1.5 cm, respectively.

The architecture of the mucosa is unchanged except basally above the muscularis mucosae. The junction between the muscularis mucosae and the mucosa is clear. The mucosal surface is slightly wavy, and, focally, presents gastric area markings. The surface is covered by narrow strands of mucus that contain a rare desquamated epithelial cell.

The surface cells contain an average amount of mucus. Their nuclei vary in shape, size, staining intensity and position. The long axes of many of the nuclei are parallel to the free surfaces of the cells. Focal pseudostratification of the nuclei is present. The basal portions of many of the surface cells contain moderately extensive vacuoles. A rare cell is vacuolated superficially. The vacuolization is not related to the amount of edema or infiltration of the papillae or the degree of congestion of their capillaries.

The papillae vary in character. Some are narrow and uninfiltated, others are wide. The latter contain a greater number of stromal cells than is usually seen—small numbers of plasma cells and lymphocytes, and scattered Russell bodies. Many of the papillae contain eosinophilic granular material (edema), a few contain a small number of extravasated red blood cells.

The majority of the neck glands are closely approximated and separated by their basement membranes and by the small amount of stroma usually present in this region. Focally, there is lymphocytic infiltration around acini of degenerative character, and increase in the number of stromal cells. The lining cells of the acini are vacuolated, their nuclei vary in size and position. Some of the acini of the neck glands are lined by cells with eosinophilic cytoplasm and pyknotic nuclei, others near the pit-junctions are dilated and lined by flattened eosinophilic neck cells and acid cells. Their lumina contain granular eosinophilic material.

Most of the peptic glands in the basal portions of the mucosa are closely approximated. There is the usual small amount of stroma between them. Those just above the muscularis mucosae are surrounded by thickened basement membranes which are focally widened, smooth and eosinophilic. The nuclei of the peptic cells of these acini vary in size and shape and in their position within the cell. Some of the nuclei are near or at the free borders of the cell despite the fasting state of the mucosa. Such dipolarity of the nuclei occurs less frequently in the superficial portions of the mucosa. A few of the acid cells of these acini contain two or three nuclei. The glandular acini in scattered areas are separated from the muscularis mucosae by finely fibrillar collagenous tissue infiltrated with lymphocytes, a small number of eosinophils and a few polymorphonuclear leukocytes. The stromal nuclei in these foci are increased. Single peptic gland acini with shrunken and degenerating acid and peptic cells are enclosed within this tissue, and merge indefinitely with it. There

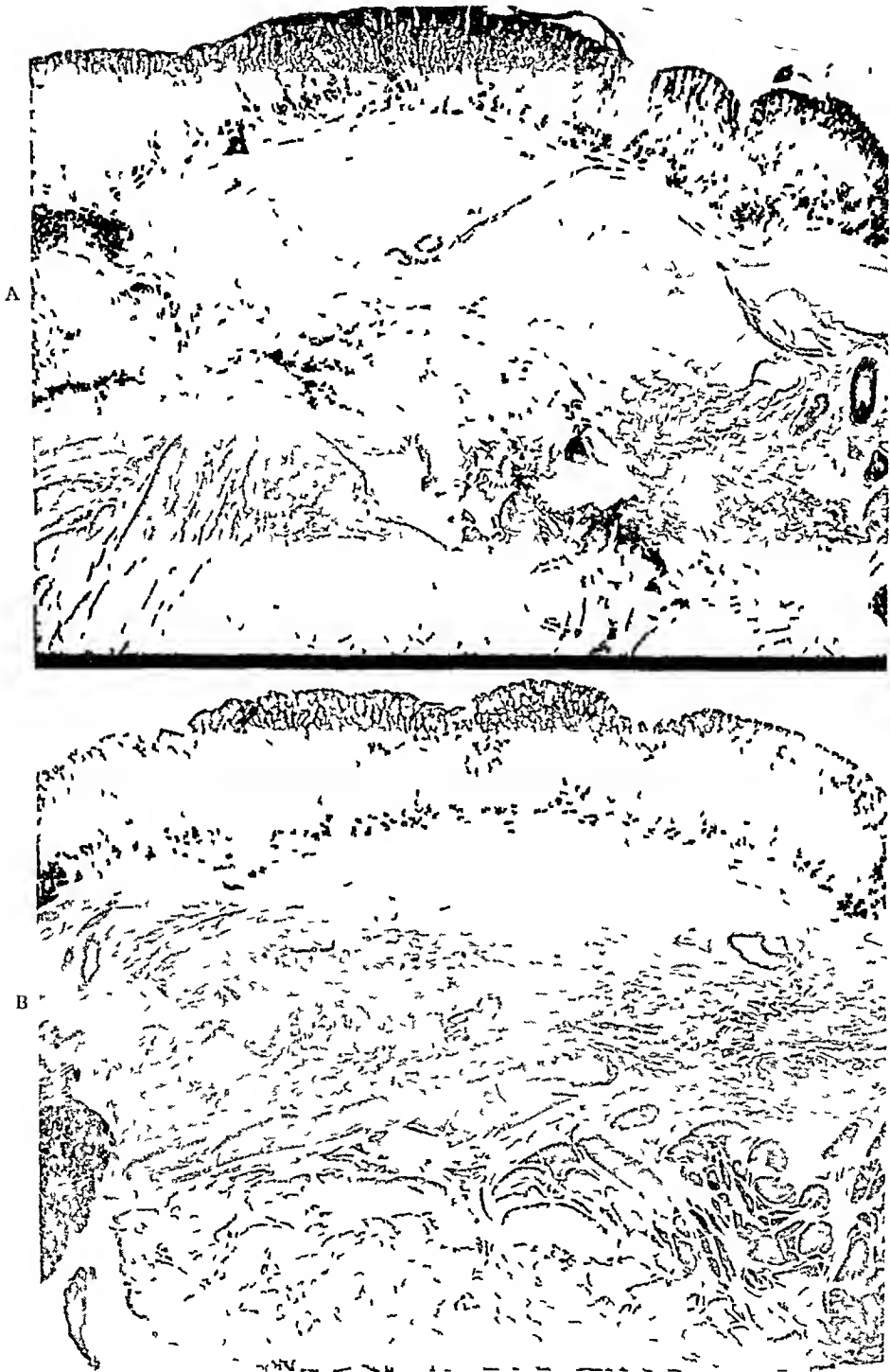


FIG 4a—Path No 75213 Original biopsy (Bouin fixed, low power) Note basal distortion in architecture (A) and edema of submucosa

FIG 4b—Path No 75213 Post resection biopsy (Bouin fixed low power) Note small lymphoid aggregate above muscularis mucosae (B) and the increased edema and congestion of the submucosa The septa of the muscularis propria are more edematous than those of Figure 4a

are a few small aggregates of lymphocytes. The muscularis mucosae is thin and is not infiltrated by cellular elements.

The degree of congestion of the mucosa varies. Most of the capillaries of the papillae are small and of uneven caliber. They measure from one to four erythrocytes in width. Below the neck gland region only scattered capillaries, one erythrocyte in width, and a rare small venule, four erythrocytes in width, are present. Above the muscularis mucosae there are dilated congested venules, empty arterioles and small foci of hemorrhage near the lines of resection of the biopsy strips. Infiltrated collagenous tissue surrounds some of these arterioles and venules.

In the submucosa there are dilated, moderately congested arteries. The veins are more dilated and more congested. A small number of lymphocytes and an occasional eosinophil are found around some of the veins. The submucosal tissue is edematous. The septa of the muscularis propria are edematous and contain a small number of lymphocytes. The serosa is without significant change.

Postresection Biopsy—Transitional Zone (see Fig. 4b). The formalin specimen consists of three strips that measure 0.7, 0.7, and 1 cm. in length, respectively; the Bouin specimen consists of four strips that measure 1, 1.2, 1.3 and 1.7 cm. in length, respectively.

The architecture of the mucosa corresponds to that of the original biopsy. The mucosal surface is covered by a narrow and in places wide, layer of denser mucus which contains a few desquamated epithelial cells and many erythrocytes. The mucus is closely approximated to the surface cells, and in a few areas cannot be differentiated from the intracellular mucus. Scattered surface cells are flatter and contain less mucus than those of the original biopsy. Focally, the surface is more wavy than in the original biopsy specimen and the gastric area markings are more discernible.

The changes noted in the neck region and in the basal portions of the mucosa in the original biopsy are found here.

The state of the capillaries in the mucosa is similar. Near the muscularis mucosae there are a few more dilated veins. Most of these contain eosinophilic granular material. Some are filled with red blood cells. There are small foci of hemorrhage around the latter just above the muscularis mucosae.

The muscularis mucosae is focally wider than that of the original biopsy specimen. It presents a small amount of edema and an occasional lymphocyte.

The submucosa is more edematous. The larger, more dilated veins within it are filled with erythrocytes; the less dilated veins and the arteries contain eosinophilic granular material and a few erythrocytes. The septa of the muscularis propria are edematous and contain a few lymphocytes. The edema extends into the bundles of adjacent muscle fibers. The serosa is slightly edematous.

Case 5—Path 75330. Male, age 46, was admitted to the hospital in June, 1941. For the past year he was treated medically for a duodenal ulcer. One week prior to admission he experienced more severe epigastric distress and during the past 24 hours noted hematemesis and melena. Wassermann—negative. Relfass' test meal—maximum free acid 60, maximum total acid 70.

The patient was prepared for operation with parenteral 5% glucose in physiologic saline. Magendie minims 6 and atropine gr. 1/150 were given hypodermically prior to anesthesia.

Operation—June 16, 1941. Under spinal and intravenous sodium pentothal anesthesia, the stomach was found to be twice its normal size. Old and recent scar tissue and edema surrounded the first portion of the duodenum. An ulcer was found on its posterior wall penetrating into the pancreas. A small diverticulum projected from the greater curvature of the duodenum. Pathologic examination of the resected specimen disclosed a penetrating duodenal peptic ulcer.

The original biopsy specimen was taken 11 minutes after incision of the abdomen, from the anterior wall of the stomach in the antral region approximately two centimeters cephalad to the greater curvature. The resected specimen was removed 16 minutes later. Two minutes after removal of the specimen sections were taken from the edges of the original biopsy wound. Both biopsies were cut into strips one millimeter in width and placed in Bouin and formalin immediately.

HISTOLOGY OF THE BIOPSIES—Original Biopsy—Antium (see Fig. 5a and 5b). The formalin specimen consists of two strips which measure 0.9 and 1.5 cm. in length, the Bouin specimen consists of two strips, each of which measures two centimeters in length.

The mucosal architecture of the major portion of each of the sections is considerably distorted by the disappearance of glandular elements and their replacement by cellular infiltration, bundles of smooth muscle fibers, and a small amount of collagenous tissue. The surface of the mucosa is wavy due to depressed, irregularly distributed, widened pits. It is covered in a few areas by narrow strands of mucus which contain rare desquamated epithelial cells and a few polymorphonuclear leukocytes.

The surface lining cells generally contain an average amount of mucus. Their nuclei vary in size, shape, staining intensity and position in the cell. The basal cytoplasm of many of the cells is narrow, elongated and separated from the neighboring cells by slit-like spaces that contain a small amount of eosinophilic, granular material. Vacuoles displace the basal cytoplasm and elevate the nuclei of a moderate number of the cells. A few larger vacuoles surround the nucleus completely and narrow the layer of supranuclear mucus. The vacuolization of the surface cells is similar over edematous and nonedematous papillae. Many of the basement membranes beneath the surface cells are widened and eosinophilic. These merge with eosinophilic, smooth material in the papillae or with the walls of underlying capillaries. In the Bouin-fixed sections the basement membranes are clearer and narrower than in the formalin-fixed sections, despite the more easily discernible edema of the papillae in the former.

The majority of the papillae are edematous, moderately wide and infiltrated by numerous plasma cells, a few are nonedematous, narrow and minimally infiltrated. The pits contain degenerating polymorphonuclear leukocytes.

The neck portions of the glands are widely separated by extensive plasma cell and lymphocytic infiltration of the stroma, and in many areas are pushed aside, or replaced, by large masses of lymphocytes. The latter form diffuse aggregates or follicles in the middle third of the mucosa. Thick, hyaline collagenous fibers occur among the lymphocytes and concentrically surround portions of the periphery of the follicles. The long axes of the adjacent displaced neck glands are oblique. Many of the neck gland acini are dilated and contain polymorphonuclear leukocytes. Their lining cells are flattened, eosinophilic and contain irregular nuclei. Many of their basement membranes are indistinct and infiltrated by lymphocytes and a few polymorphonuclear leukocytes. A moderate number of argentaffin cells are found among the neck gland acini.

Large areas of the basal portions of the mucosa are completely replaced by dense masses of lymphocytes. These present a moderate number of secondary centers (follicle formation). They contain reticulum cells, dense, hyaline, collagenous fibers and groups of smooth muscle fibers. Some of the lymphoid aggregates occupy the lower third of the mucosa, others are so extensive that they reach the pit region. They enclose islands of degenerating glandular acini with vacuolated cytoplasm and deformed nuclei. Antral glands adjacent to the large lymphoid aggregates are pushed aside. Their long axes, originally perpendicular, are now almost parallel to the surface of the mucosa.

Between the masses of lymphocytes the relationship of the remaining antral glands to the muscularis mucosae and the stroma differs. The bases of a small number reach



FIG 51—Path No 75330 Original biopsy (Boun fixed, magnification 62 times) Note the marked distortion of mucosal architecture and the basal lymphoid aggregates Basal vacuolization of the surface cells (A) Small groups of cells (B) remain in the altered stroma
 FIG 52—Path No 75330 Original biopsy (formalin fixed, magnification 62 times) Note complete replacement of antral and neck glands by large lymphoid follicle (atrophic infiltrative gastritis) The neck glands (A) and the antral glands (B) adjacent to the follicle are pushed aside Their axes are changed The muscularis mucosae (C) is infiltrated by lymphocytes
 FIG 53—Path No 75330 Post resection biopsy (Boun fixed, magnification 62 times) The features are essentially similar to those described in Figure 51 Note the greater amount of submucosal edema

the muscularis mucosae, others are separated from the muscularis mucosae by a small amount of fine collagenous tissue infiltrated by lymphocytes, plasma cells and some eosinophils and polymorphonuclear leukocytes. Russell bodies are scattered through both this tissue and the areas of marked infiltration. In a few places above the muscularis mucosae the antral glands are replaced by dense collagenous tissue infiltrated by lymphocytes. The width of the muscularis mucosae is increased by moderate edema and lymphocytic infiltration. At some points beneath the large aggregates, lymphocytes replace the muscle fibers and destroy their continuity.

Congested capillaries, one to three erythrocytes in caliber, are noted at the summits of scattered papillae. A few capillaries, three to six erythrocytes in width, are at the level of the pit-neck junctions. The remainder of the mucosa is relatively bloodless. A rare small vein penetrates the muscularis mucosae. Within the latter there are some nondilated arterioles and venules filled with erythrocytes.

The submucosa is edematous and contains dilated arteries and veins filled with erythrocytes. A group of lymphocytes surrounds one vein. Lymphocytes from the large mucosal aggregates extend through the muscularis mucosae into the submucosa. The collagenous fibers superficial to the muscularis propria are denser than elsewhere and parallel to the mucosal surface.

The septa of the muscularis propria are slightly edematous. The serosa is without significant change.

Postsection Biopsy—Antrum (see Fig 5c). The formalin specimen consists of four strips. Two of these each measure 0.8 cm in length, the other two each measure 2.5 cm in length. The Bouin specimen consists of four strips which measure 0.6, 1.3, and 1.6 cm, respectively.

The mucosal architecture corresponds closely to that of the original biopsy.

The surface of the mucosa is covered by narrow and wide layers of denser mucus which contains desquamated epithelial cells, erythrocytes and single and clumped polymorphonuclear leukocytes. In some areas the mucus incises with the intracellular mucus of the surface cells so that but a narrow, eosinophilic zone of cytoplasm remains. This is either anuclear, or contains a deformed, shrunken or swollen, poorly demarcated nucleus. The boundaries between the surface cells in these areas are not distinguishable. Erythrocytes and lymphocytes in greater numbers are found between and within the surface cells than in the original biopsy. More of the surface cells are basally vacuolated but the degree of vacuolization is similar.

The pits are slightly longer. In the neck glands a few regular mitoses are present. The argentaffine cells are slightly more numerous.

The type and degree of infiltration and the alteration of the neck and antral glands correspond to that of the original biopsy. The eosinophils in the muscularis mucosae are slightly more numerous. The edema of an occasional papilla is greater. Focally, there is greater edema above the muscularis mucosae and between groups of its muscle fibers. The remaining coats of the gastric wall are more edematous.

Congested capillaries at the summits of the papillae are more numerous but are of the same caliber (one to three erythrocytes in width). At the pit-neck junctions congested capillaries three to six erythrocytes in width and congested venules eight to ten erythrocytes in width are more numerous. The deeper portions of the mucosa, as in the original biopsy, are relatively bloodless except for an occasional perpendicular congested venule (six to eight erythrocytes in width) which runs superficially from the muscularis mucosae. A few venules, three erythrocytes in width, and a few contracted arterioles are present above the muscularis mucosae. The submucosal veins and the capillaries of the septa of the muscularis propria are more congested. Focal hemorrhage occurs in the submucosa and the septa of the muscularis propria.

COMMENT

A study of Table III demonstrates quite clearly and conclusively that the fundamental histologic architecture of the biopsy specimens taken prior and subsequent to resection was not essentially altered by the operation of subtotal gastrectomy *per se* in any of the 35 cases which were analyzed. It should be remembered, however, that the number and distribution of the infiltrating cells varied in many of the biopsy strips from the same specimen, but such differences in adjacent mucosal areas have been found to be common.

However, the surgical procedure did produce changes in the surface of the mucosa, alterations in the amount of tissue fluid throughout the entire gastric wall, and congestion of the blood vessels. The amount of surface mucus increased and the volume of intracellular mucus decreased as the interval lengthened between the original biopsy and the resection of the specimen. In a few instances in which this interval exceeded 20 minutes, the intracellular mucus merged with that on the surface. However, the loss of this intracellular mucus rarely produced significant cytoplasmic or nuclear changes in the surface cells. Minor changes in the shape and height of the papillae and in the width and contour of the pits were observed. When alterations of the surface cells, including basal vacuolization, focal pseudostratification (piling), variation in the position, shape and staining intensity of the nucleus were noted in the original biopsy, they were also present in the postresection specimens. In some of these cases there were small numbers of polymorphonuclear leukocytes around the neck glands or in the papillae in the postresection biopsies.

Stromal edema and capillary congestion of the papillae, and edema of the stroma superficial to the muscularis mucosae were more evident in the postresection biopsy, except in one case (Case No. 75918), in which the basal edema was less intense. Generally, the muscularis mucosae was more edematous. It should be noted that the edema was most striking in the submucosa and in the adjacent septa of the muscularis propria when the interval between the biopsies exceeded 20 minutes.

Hemorrhage involving the entire mucosa occurred mainly near the edges of the original biopsy. This was present regardless of the time interval between the original biopsy and the resection. The glandular acini were separated by the extravasated blood but remained intact except in No. 70421, in which desquamation of the apical cells was present. In No. 76566 a small number of surface cells were destroyed over one hemorrhagic papilla. Submucosal hemorrhage was more striking and most marked when the intervals exceeded 20 minutes. The hemorrhage involved mainly those portions of the submucosa just beneath the muscularis mucosae and above the muscularis propria. In Case I, Path No. 70308, in which but ten minutes elapsed between the original biopsy and the resection, the submucous hemorrhage was quite extensive. The veins of the submucosa, and the capillaries and venules of the septa of the muscularis propria were more congested in the postresection

biopsy The walls of some of these vessels were infiltrated and surrounded by polymorphonuclear leukocytes

CONCLUSIONS

1 No histologic differences of diagnostic significance were found in this series of 35 cases in which preliminary and postresection biopsies were carefully studied and compared

2 Postresection specimens, if fixed immediately, represent, with minor modifications, the histologic state of the gastric wall existent prior to resection

REFERENCE

- ¹ Gitlitz, A J, and Lerner, H H Interpretation of Gastroscopic Observations in Terms of the Histology of the Gastric Mucosa Presented before the section on Gastro-Enterology and Proctology, A M A Session, June 12, 1940

THE EFFECT ON GASTRIC ACIDITY OF GASTRO-ENTEROSTOMY AND GASTRIC RESECTION FOR PEPTIC ULCER*

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IT IS IMPORTANT TO KNOW, if possible, the underlying reasons for performing gastro-enterostomy and gastric resection for peptic ulcer. Particularly in a teaching clinic, engaged in training young surgeons, we should know why we advocate the surgical methods which we teach and how they achieve their effects. I need not, before this audience, take the time to discuss the reasons commonly advanced to explain why these procedures are effective or why they fail. In more recent years, as you are aware, the etiologic relationship between excessive acid and ulcer has been emphasized through the experimental and clinical work of Dragstedt, Wangensteen, and many others, whose important work deserves more consideration than can be given it in so short a presentation. As a result of this work some authors believe that the empiric surgical approach to the problem of ulcer in man can be abandoned and may now be approached scientifically on the basis that the acid secreted by the stomach is the important factor in the causation of ulcer. Surgical procedures, therefore, which abolish or diminish acid gastric secretion may be expected, on this basis, to cure ulcer and prevent recurrence. It has been observed by a number of authors that gastro-enterostomy fails to alter acid secretion. It does not, therefore, to many, meet the requirements of a surgical operation designed to cure ulcer, even though there is abundant evidence in the literature that it relieves the symptoms and protects the individual against the complications of ulcer in a fairly high percentage of cases. It has also been observed that gastric resection, if of sufficient magnitude, does diminish or abolish acid secretion and, therefore, more nearly meets the requirements of an ideal operation for the cure of ulcer. Certain authors have gone farther in their approach to the problem and find that not only resection, but specific types or methods of resection assure achlorhydria more certainly than others. Thus, for example Wangensteen has found that with a resection of three-fourths of the stomach, and according to the Hofmeister or Finsterer exclusion method (the latter with excision of antral mucosa), 63 per cent of his patients are achlorhydric, and fail to develop gastrojejunal ulcer.

It will be observed that the recent emphasis has been laid upon actual reduction or diminution of acid secretion by the removal of secretory gastric mucosa. The factors of dilution and neutralization of acid through surgical procedures—another possible explanation for their success if acid is the

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important factor in the causation of ulcer—have not recently received much attention. Yet Dragstedt, and others, have shown that food, pancreatic juice, gastric and intestinal mucus, duodenal juice and bile, dilute and neutralize the acid and together probably account for the fact that the stomach does not constantly digest itself. There seems no reason to believe that successful dilution and neutralization of acid may not be as effective a means of combating ulcer as actual reduction in acid. In gastro-enterostomy we know that postoperatively the acid gastric secretion is only rarely significantly reduced, yet the operation, in our hands and in the hands of many others, gives satisfactory results over a long-term follow-up period in 75 to 80 per cent of cases. In gastric resection the changed conditions created are much the same as in gastro-enterostomy. There is an artificial stoma without sphincteric control, opportunity for rapid emptying of the stomach, possibility of regurgitation of alkaline intestinal contents and, therefore, of dilution and neutralization of acid. The removal of acid-secreting mucosa, the result of resection may well be an added advantage of the operation in that it may reduce the total volume of acid secreted. But the factor of dilution and neutralization remains as a reason for the beneficial effects of resection and it is possible that the effect of reduction of acid has been overemphasized. The matter has more than academic interest. The idea that acid is the important factor in the genesis of ulcer may be sound, but the idea of controlling the production of acid by larger and larger resections has already led us to sacrifice the greater part of an often normal organ without solving the problem of ulcer and with a mortality which must be considered. We believe that the subject warrants further study.

In the course of a study of some 1200 patients with peptic ulcer admitted to our wards in the past ten years, we have assembled those patients who have been subjected to operation and who have had careful pre- and postoperative acidity determinations made. The determinations all have been made by the junior author and according to the histamine method of Bloomfield and Poland. Only patients in whom the junior author is satisfied that both pre- and postoperative acidity determinations are above reproach are included in this presentation. The determinations extend over a period up to seven years after operation, and in many cases have been repeated over the years. The credit for this work belongs, then, to the junior author, the senior author having merely collected and tabulated the data and drawn such conclusions as seemed justified. The purpose of the study has been (a) to determine the effect of gastro-enterostomy and gastric resection upon acid secretion, (b) to determine the acid secretion according to the magnitude of gastric resection, (c) to determine the results of operation in relation to the postoperative acid secretion, and (d) to determine the results of operation regardless of the acid secretion.

I GASTRO-ENTEROSTOMY

Seventy-five patients with gastro-enterostomy for gastric and duodenal ulcer, the latter predominating, have been studied. In all the pre- and post-

operative acidity determinations are satisfactory and reliable. The results are shown in Charts 1 and 2. In Chart 1, showing the postoperative acidity determinations following gastro-enterostomy, it is observed that of the 75 patients, 69 or 92 per cent, show free hydrochloric acid equal to and, in the large majority, greater than normal (60° free HCl), while but six, or eight per cent, have acidities below normal. The average postoperative acidity for the 75 patients is 82° free HCl. In Chart 2, showing the pre- and postoper-

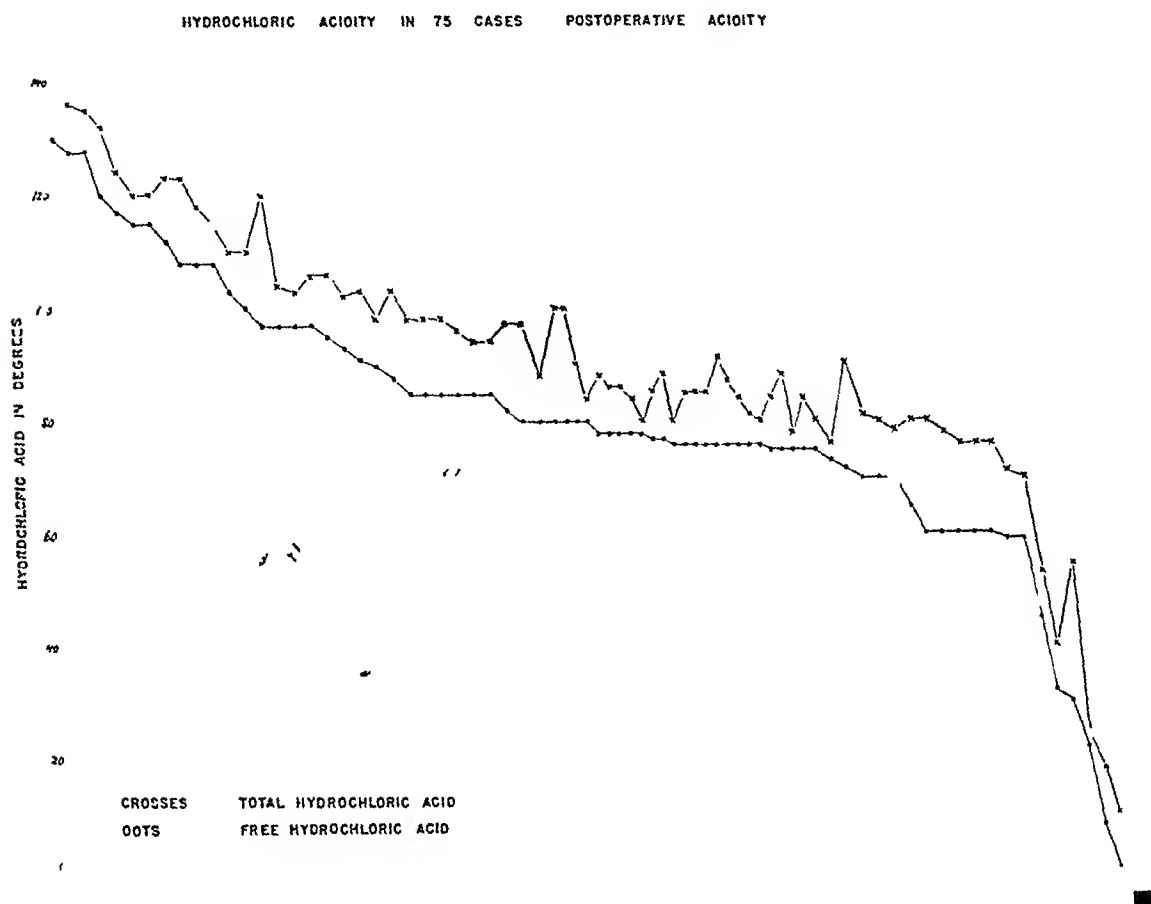


CHART I Determinations of gastric acidity in 75 patients after Gastroenterostomy

ative acidities of 50 patients particularly and repeatedly studied, it will be observed that in 28, or approximately one-half of the cases, the preoperative acidity is slightly higher than the postoperative, in 22, the postoperative acidity is higher than the preoperative. In only five patients is there a significant diminution in acidity following operation. The average preoperative acidity for 50 patients is 90° free HCl, excluding the five patients, the average postoperative acidity is 88° free HCl. In the series, the interval of time between operation and postoperative gastric analysis does not appear strikingly to influence the findings, although it should be said that for the majority of patients the interval between operation and the last gastric analysis is less than five years. Regardless of the manner in which the clinical results are compared with the acidity, there does not appear to be any correlation between them. Of the 75 patients studied, 56, or 75 per cent, after a period of follow-up of from six to ten years, have satisfactory results following

gastro-enterostomy, and in the presence of postoperative acidities which vary between 0° and 132° free HCl. Nineteen, or 25 per cent, have unsatisfactory results, and in the presence of acidities which vary between 50° and 130° free HCl.

From a study of these 75 patients, then, it would appear that gastro-enterostomy affects the acid secretion of the stomach only in exceptional cases. Moreover, it appears that the satisfactory and unsatisfactory results

PREOPERATIVE AND POSTOPERATIVE ACIDITY IN 50 PATIENTS

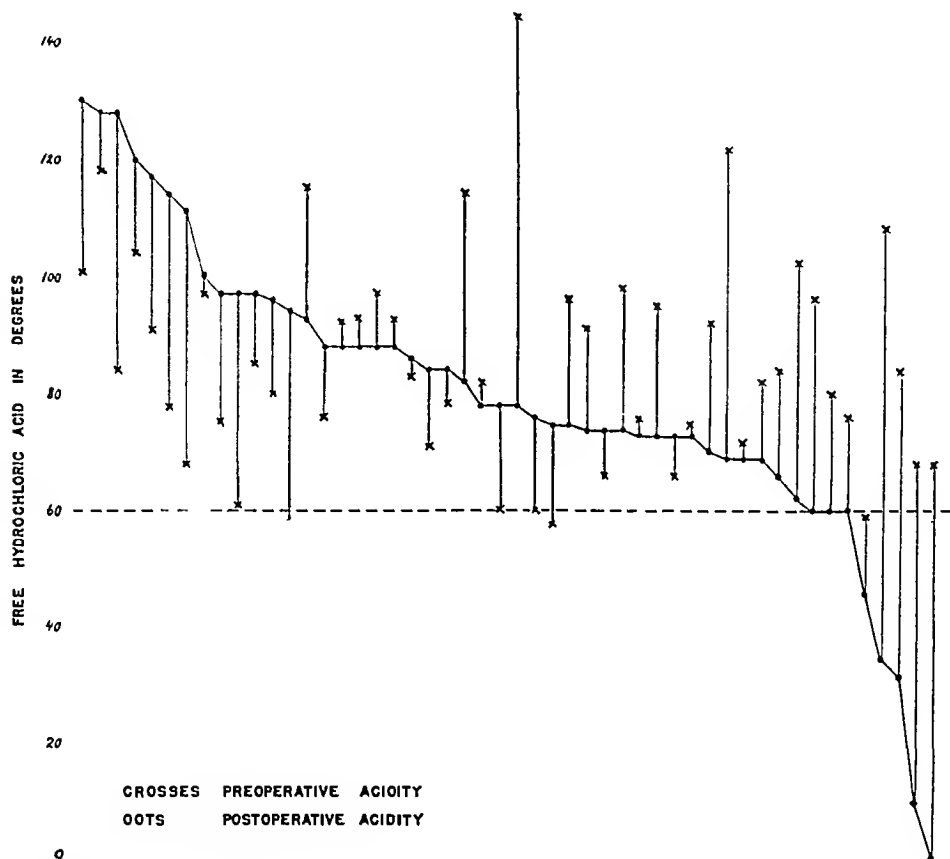


CHART II Determinations of pre and postoperative gastric acidity in 50 patients treated by Gastroenterostomy

following operation can not, to any considerable degree, be related to the secretory activity of the stomach. If a high acid is the important etiologic factor in the genesis of ulcer and the cause of its perpetuation or its recurrence, then gastro-enterostomy achieves its results probably by more rapid and complete dilution and neutralization of acid.

II GASTRIC RESECTION

Eighty-eight patients with gastric and duodenal ulcer subjected to gastric resection have been studied. Of these, 63 had duodenal and 25 gastric ulcers. They were subjected to resection of varying magnitudes. Thirty-one patients had what may be called a minimal resection—less than one-half of the

stomach but including the antrum, pylorus and ulcer bearing duodenum—46 patients had what may be termed a moderate resection—one-half to two-thirds of the stomach—and 11 patients had a major resection—over two-thirds to three-quarters of the stomach, or more. The results of these resections, which were chiefly according to the Billroth-II, Polya or Hofmeister methods, are shown in Tables I, II and III, and are summarized as follows

TABLE I

THE EFFECT OF GASTRIC RESECTION IN RELATION TO ACID GASTRIC SECRETION IN 63 PATIENTS WITH DUODENAL ULCER HAS BEEN A POSTOPERATIVE ANACIDITY IN 17 OR 27 PER CENT, A LOW ACID (BELOW 60° FREE HCL) IN 15 OR 23.8 PER CENT, AND NO SIGNIFICANT CHANGE IN ACIDITY (60° FREE HCL OR MORE) IN 31 OR 49.2 PER CENT. THE THREE GROUPS WITH ANACIDITY, LOW ACID AND NO CHANGE IN ACID ARE ANALYZED AS FOLLOWS

GROUP I 17 PATIENTS HAVING A POSTOPERATIVE ANACIDITY, OR ACHLORHYDRIA

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	0		
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	16	14 (87.5%)	2 (12.5%)
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	1	1 (100%)	

GROUP II 15 PATIENTS HAVING POSTOPERATIVELY A LOW ACIDITY

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	4	4 (100%)	
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	9	9 (100%)	
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	2	2 (100%)	

GROUP III 31 PATIENTS HAVING POSTOPERATIVELY AN ADEQUATE OR HIGH ACIDITY

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	21	18 (85.7%)	3 (14.3%)
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	9	7 (77.7%)	2 (22.3%)
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	1	1 (100%)	

TABLE II

THE EFFECT OF GASTRIC RESECTION IN RELATION TO ACID GASTRIC SECRETION IN 25 PATIENTS WITH GASTRIC ULCER HAS BEEN A POSTOPERATIVE ANACIDITY IN 18, OR 72 PER CENT, A LOW ACID IN FIVE OR 20 PER CENT, AND NO CHANGE IN ACIDITY IN TWO OR EIGHT PER CENT. THE THREE GROUPS WITH ANACIDITY, LOW ACID AND NO CHANGE IN ACID ARE ANALYZED AS FOLLOWS

GROUP I 18 PATIENTS HAVING A POSTOPERATIVE ANACIDITY

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	2	2 (100%)	
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	9	9 (100%)	
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	7	7 (100%)	

GROUP II 5 PATIENTS HAVING POSTOPERATIVELY A LOW ACID

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	2	2 (100%)	
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	3	2 (66.6%)	1 (33.3%)
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	0		

GROUP III 2 PATIENTS HAVING POSTOPERATIVELY NO CHANGE IN ACIDITY

Extent of Resection	Number of Cases	Satisfactory Clinical Results	Unsatisfactory Clinical Results
Less than $\frac{1}{2}$ of stomach	2	2 (100%)	
$\frac{1}{2}$ to $\frac{3}{4}$ of stomach	0		
Over $\frac{3}{4}$ to $\frac{3}{4}$ or more	0		

TABLE III

SUMMARY OF TABLES I AND II—88 PATIENTS WITH DUODENAL AND GASTRIC ULCER

Extent of Resection	Number of Cases	Number with Anacidity	Number with Low Acidity	Number with Normal or High Acidity	Satisfactory Clinical Results	Unsatisfac- tory Clinical Results
Less than $\frac{1}{2}$ of stomach	31	2 (6.4%)	6 (19.3%)	23 (74.3%)	28 (90.3%)	3 (9.7%)
$\frac{1}{2}$ to $\frac{2}{3}$ of stomach	46	25 (54.3%)	12 (26%)	9 (19.6%)	41 (89.1%)	5 (10.9%)
Over $\frac{2}{3}$ to $\frac{3}{4}$ or more	11	8 (72.7%)	2 (18.1%)	1 (9.2%)	11 (100%)	

(a) Of 31 patients with minimal gastric resections eight, or 25.7 per cent, show postoperatively a low acidity (less than 60° free HCl), of whom two have an anacidity, while 23, or 74.3 per cent, have an adequate or high acidity (60° free HCl, or more). The follow-up of these 31 patients shows that 28, or 90.3 per cent, have satisfactory results three, or 9.7 per cent, have unsatisfactory results.

(b) Of 46 patients with moderate resection, 37, or 80.4 per cent, show postoperatively a low acidity, of whom 25 have an anacidity, while nine, or 19.6 per cent, have an adequate or high acidity. The follow-up of these 46 patients shows that 41, or 89.1 per cent, have satisfactory results, five, or 10.9 per cent, have unsatisfactory results.

(c) Of 11 patients with major resection ten, or 90.8 per cent, show postoperatively a low acidity, of whom eight have an anacidity, while one, or 9.2 per cent, has an adequate acidity. The follow-up on these 11 patients shows that all, or 100 per cent, have satisfactory results.*

Although the number of major resections is too small to be conclusive, the above findings indicate (a) that gastric resection does reduce acid gastric secretion, and in direct proportion to the extent of the resection, and (b) that patients with postoperative low acidity, or anacidity, have, as a group, had better results by ten per cent than those with an adequate or high acidity.

But the study shows, also, that the satisfactory results from resection do not parallel the gastric acidity. The results of minimal resection, following which only 25 per cent of patients have an acidity below normal, are as good as those of moderate resection, following which 80 per cent of patients have an acidity below normal. The results of major resection following which 90 per cent of patients have a low acidity, are better than those of minimal and moderate resection in the small group of 11 patients here presented, but I feel reasonably sure will not prove to be when we include the major resections of those patients whose results we know, but whose acidity studies have not been completed. Again, if we compare the results in all patients who, postoperatively, have a low acidity, with the results of minimal, moderate and major resections, regardless of the resulting acidity, we find that they approach within five per cent of each other.

It would appear then, from our experience, (1) that subtotal gastric resection, of whatever magnitude or method, does not ensure an achlorhydria, (2) that the beneficial effects of gastric resection are not necessarily

* Of the 88 patients with gastric resection, 50 have been followed one to two years, 30, two to five years, and eight, five to ten years.

due to the reduction in acid secretion but commonly are obtained, as in gastro-enterostomy, in the absence of significant change in acidity, and (3) that the chances of ensuring either achlorhydria, or significantly better results, by increasing the magnitude of resections beyond a moderate resection are rather small. There are objections to major resection. The mortality in the hands of the majority of surgeons is rather high. It does not prevent recurrent ulceration, particularly in duodenal ulcer, and it makes difficult and hazardous any further surgery if recurrent ulceration takes place.

SUMMARY AND CONCLUSIONS

1. A study of the pre- and postoperative acidities in 163 patients with peptic ulcer subjected to gastro-enterostomy or gastric resection shows that, postoperatively, 61, or 37.4 per cent, have achlorhydria or low acidity, while 102, or 62.6 per cent, have an adequate or high acidity. In the presence of these acidity findings, 136, or 83.4 per cent, of the patients have satisfactory clinical results. This lack of correlation between acidity and results leads us to doubt that a reduction in acid secretion is the sole factor in achieving the results in these two types of operation.

2. Following gastro-enterostomy there is no significant change in acid secretion, yet in this series of 75 patients, 75 per cent have satisfactory results over a follow-up period of six to ten years. It must be presumed that dilution and neutralization of acid rather than reduction in acid is the effective means of achieving these results, if acid is the important factor in the genesis of ulcer.

3. Following gastric resection there is, in general, a reduction in acid secretion in proportion to the extent of the resection. But resection of any magnitude, consistent with a reasonable mortality, does not, in our experience, ensure achlorhydria. Moreover, when we compare the clinical results with the acidity, we again find a lack of correlation, for in minimal resection, as above described, 90 per cent of the patients have satisfactory results, while 25 per cent have a reduction in acid. It is probable that in resection, also, dilution and neutralization of acid are important factors in the results obtained.

4. If these findings are confirmed by others, it would appear of doubtful value to pursue the idea of ensuring achlorhydria and, therefore, better results by larger and larger resections. It may be better to accept the limitations of resection as a treatment of ulcer and adopt an operation of lesser magnitude which ensures fairly satisfactory results with a reasonable mortality and permits further surgery if recurrence takes place.

5. The findings presented do not controvert the etiologic relationship between acid and ulcer. It is possible that operations other than those discussed, which are now being tested in our department, may not only support the present evidence of this relationship but achieve a reduction in acid more constantly than does gastric resection.

CHOLECYSTO - ENTEROSTOMY, CHOLEDOCHO - ENTEROSTOMY AND ENTERO-ENTEROSTOMY BY MEANS OF RUBBER BANDS THE USE OF RUBBER BANDS IN THE MIKULICZ OPERATION*

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AND

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A SPECIAL RUBBER CORD was used by Theodoie A McGiaw¹ more than 50 years ago in gastric and intestinal surgery. The stomach wall is thick and not very satisfactory for this technic. The contents of the stomach and upper small intestine usually have but few bacteria, and an adequate communication between them can best be made by incision and suturing. However, there seems to be a place for a practically aseptic closed technic in which an opening can be established between viscera with highly septic contents. If this can be done with ordinary rubber bands instead of special elastic cords and special instruments, it would seem desirable.

We have performed nine experiments upon dogs, anastomosing the limbs of a loop of small bowel to each other or the small bowel to the cecum. In two experiments, after 24 hours there was slight necrosis of the tissue and in one, a small fistulous opening. After 48 hours there was a larger fistulous tract. In other dogs, after two weeks, there were no symptoms of obstruction even when the loop of bowel between the application of the band was occluded. In three of the experiments the rubber band was surrounded with catgut suturing. In six there was no suturing, the band alone was used. In none of the experiments was there any evidence of peritonitis or leakage.

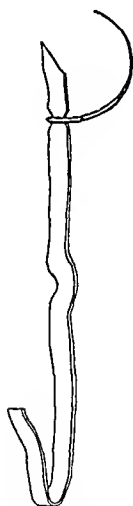


FIG 1.—This drawing shows the needle threaded with No. 32 stationer's rubber band cut obliquely. The needle and band are dipped in a solution of iodine just before being used. The end is then clamped with hemostatic forceps so that the band can be applied under tension.

In both experimental and clinical work the ordinary stationer's No. 32 rubber band is cut obliquely and threaded into a large, curved needle without a cutting point, formerly called a catgut needle (Fig 1). Two segments of bowel, or the bowel and the gallbladder, are first united with a continuous suture of fine chromic catgut (Figs 2 and 8). The rubber band with the needle is dipped into iodine solution just before being used. A long, deep bite is taken in one loop of the viscus. The end of the band is clamped with a hemostat. The band is drawn through under considerable tension. A second bite is taken in the apposing viscus in the opposite direc-

* Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

tions (Figs 3 and 9) A bite of three to five centimeters may be easily obtained by puckering the bowel so the needle can catch a much longer bite than if the bowel were held smooth (Fig 8)

While in six experiments there was no suturing and no leakage, clinically, it seemed safer, and added very little to the time and difficulty of the operation, to surround the band with a continuous suture of fine chromic catgut In the clinical cases, also, there has been no leakage In all of the clinical cases the band has been reinforced by suturing In two patients upon whom an entero-enterostomy was performed, and the patients died from other causes, it was found that the band had not cut through in one case, Mr A F D (Case No B-8307), eight days after operation, and there was only a very small opening between the loops in another case, Mr W P M (Case No B-9726), 11 days after operation In these two cases only a single band was used In one other case, Mrs N G N (Case No C-2415), the triple band technic was used to by-pass a small segment of bowel injured by a femoral hernia The bowel was not gangrenous The second and third bands were very small and no incision in the peritoneum embraced by the rubber band (as is now done) was made Four days later there was obstruction, the loop of bowel with the bands was resected and the patient recovered satisfactorily The specimen showed the bands had not cut through Although this was only four days after the operation it was contrary to our experience in the experimental work, for in all of the dogs after 48 hours there was a fistulous tract between the apposed bowels, though in some it was rather small Therefore, we modified the clinical procedure, for it was apparent that when the apposing walls of viscera are brought together by the rubber band, tissue is compressed with the peritoneal surfaces in intimate contact This makes for strong union of the portion of bowel within the grasp of the band and the compressed tissues heal together firmly and solidly and may offer such resistance that a fistulous opening does not form

The technic as now employed is as follows The apposing viscera are united with a row of continuous sutures of fine chromic catgut (Figs 2 and 8) A No 32 rubber band is passed, as described, while sufficient tension is made on the band to reduce its size If the end of the band is clamped and firmly held while the band is being passed under traction, when the traction is released, the band enlarges, fills the needle hole, and prevents leakage This makes the procedure practically aseptic In one case, the anastomosis was made with the gallbladder and, when fine chromic catgut sutures were passed between the gallbladder and the bowel, there was slight leakage of bile though when the band was passed through the bowel and the gallbladder there was no leakage The rubber band is carried through the viscera to be united, but it is not tied (Figs 3 and 9) Then a second No 32 rubber band, in the same type of needle is passed through the bite in the bowel made by the first band on one side and a third band is similarly passed on the opposite side An in-



FIG 2—The first step in cholecystojejunostomy. A loop of jejunum about two feet from its origin is brought through the transverse mesocolon. If the transverse mesocolon is short and fat, it can be brought over the transverse colon. The jejunum is fastened to the gallbladder with a continuous suture of fine chromic gutgut.

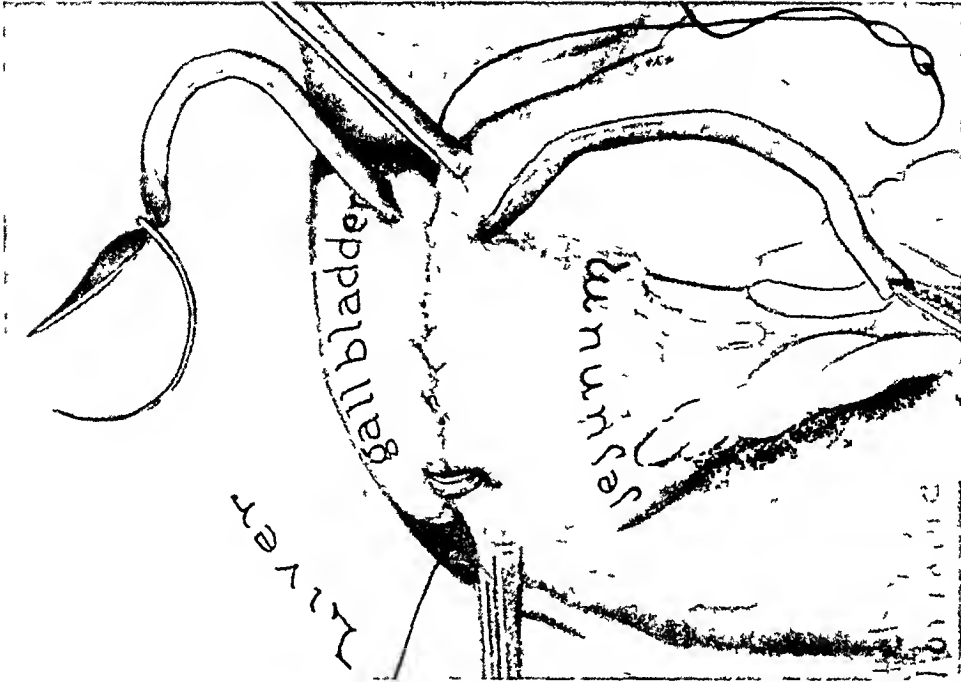


FIG 3—A No. 32 rubber band is passed first through the jejunum and then in the reverse direction through the gallbladder.

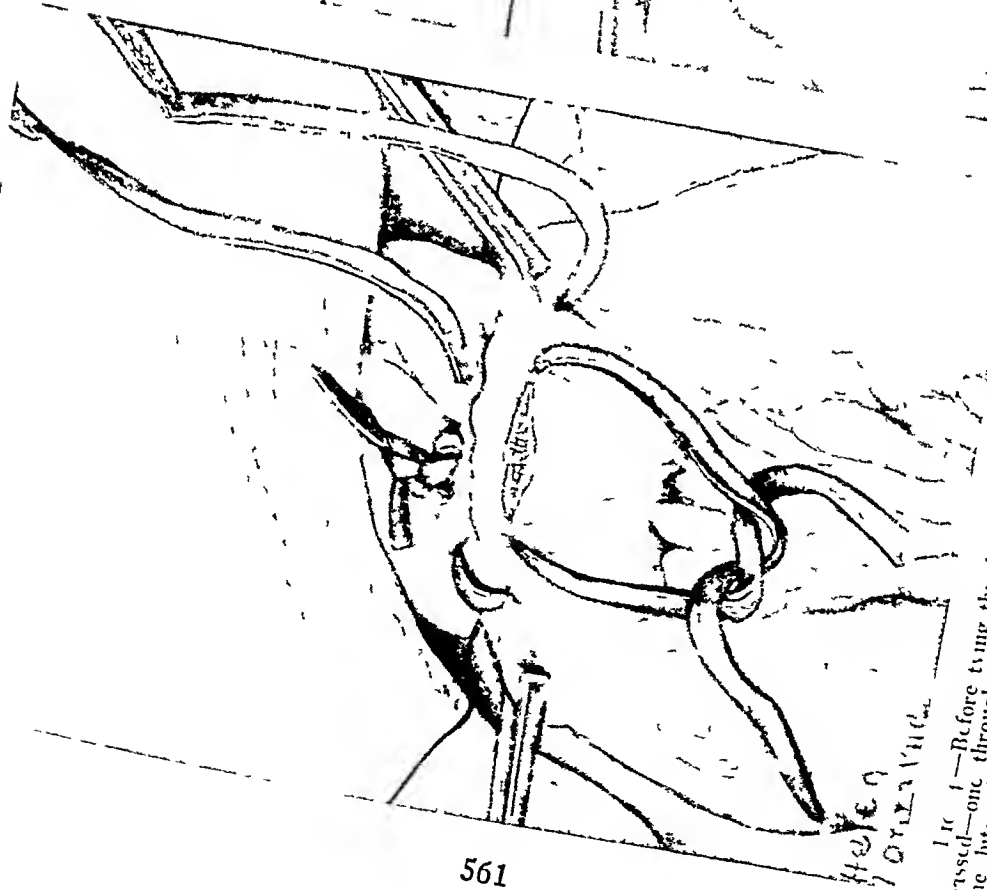


Fig. 1—Before tying this band, however, two other bands are passed—one through the portion of jejunum that is embraced in the loop of the first band and a third band catching the portion of the jejunum that the first band embraces. An incision is made in the jejunum through the peritoneum and a portion of the muscular coat, taking care not to penetrate the lumen of the bowel. The third band which has been applied to the gallbladder is tied snugly without the necessity of incising the peritoneum.

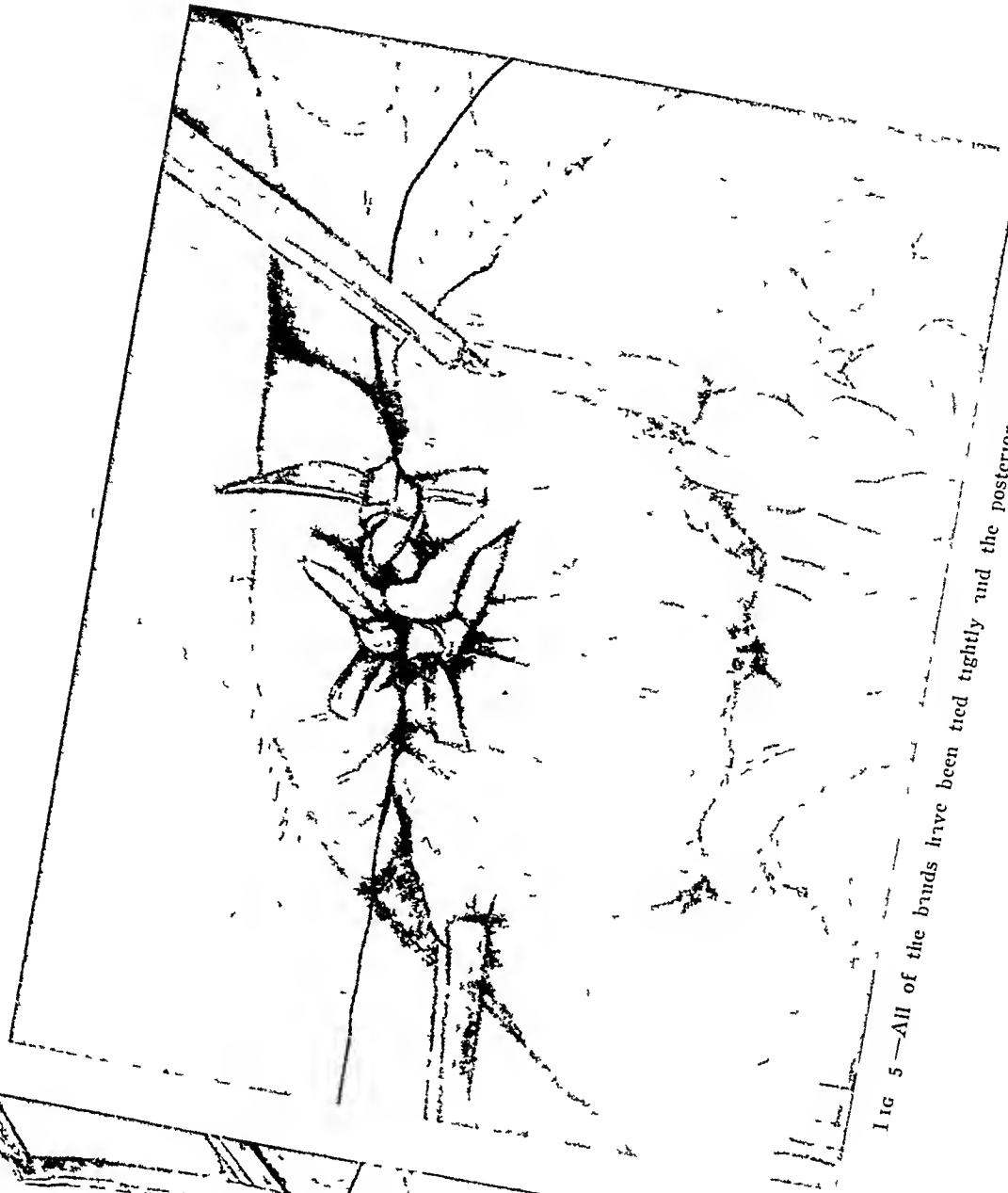


Fig. 5—All of the bands have been tied tightly and the posterior suture is taken up.

cision is made through the peritoneum and some of the muscular coat of that portion of the bowel within the grasp of the last two bands and each of these bands is tied down snugly (Figs 4 and 10). Then the first band is tied several times very tightly (Figs 5 and 11). The suturing around the rubber band is completed (Fig 6).

In this manner the situation as regards compression of the apposing surfaces is materially altered. Instead of having two peritoneum-covered surfaces approximating each other under heavy pressure, with the optimum conditions for stout union, the inner rubber bands prevent this union, not



FIG 6—The posterior suture has been completed anteriorly and is tied to its original end. In addition, a series of interrupted mattress sutures is placed. The ends are left long and a tag of omentum or peritoneum covered fat is carried around the anastomosis and fastened in position by passing through it the long ends of the mattress sutures.

only by preventing approximation of the peritoneum of the apposing viscera, but their own compression in each loop of the viscera makes independent openings. The incision in the peritoneum also aids in establishing an opening. In the triple rubber band technic suturing is essential.

From May 15, 1941 (the first case) to January 1, 1943, the rubber band operation has been performed 19 times on 18 patients. The technic with a single rubber band was used in nine operations, and with the triple rubber bands in ten operations. In all of the recent cases the triple rubber bands have been employed.

The indications for this operation may be classified under four heads
(1) *For obstruction of the terminal portion of the common duct.* When



FIG 7—Cholecystojejunostomy. The jejunum has been sutured to the common bile duct. A rubber band has been passed through the apex of the loop of jejunum and in a reverse direction through the common bile duct. Along the dotted line an incision through the peritoneum and part of the muscular coat of the bowel is made. The rubber band is tied down tightly and the suture is taken up carried forward and tied to its original end. Interrupted mattress sutures of fine chromic catgut are placed and omentum or peritoneum covered fat is brought around and fastened as in the cholecystojejunostomy. The lateral anastomosis or enteroenterostomy is in a stage of completion. The first rubber band has been placed. The second and third rubber bands are also in position. The peritoneum and superficial portion of the muscular coat are incised along the dotted line. On the left this incision has been made and one of the rubber bands has been tied. The rubber band on the right side is to be tied and then the first rubber band is tied snugly. The continuous suture is carried forward and tied to its original end.

the obstruction is from a calculus, the stone should be removed even though the duodenum must be incised, and this usually suffices. But in obstruction from a malignant growth in the head of the pancreas or in the ampulla of Vater, when a radical operation does not appear wise, or in obstruction from a benign lesion, such as a stricture, this procedure is indicated. However, it is subdivided into (a) cases in which the gallbladder is present (Fig 2), and (b) cases in which the gallbladder has been previously removed (Fig 7). We have had cases under both of these subheads.

(2) *Intestinal obstruction*

(3) *Entero-enterostomy as an adjuvant to anterior gastro-enterostomy or to total gastrectomy*

(4) *In the Mikulicz-type of operation*

(1a)—In terminal obstruction of the common duct when the gallbladder is present and its exploration is desired, the gallbladder may be emptied with a trocar and cannula, incised, and explored with the finger. The incision is closed with a purse-string suture and the technic is then applied as though the gallbladder had not been opened. The exploration may be unnecessary. The excellent procedure of Brunschwig,² who, in excision of the duodenum or head of the pancreas for cancer, brings over a loop of jejunum and anastomoses it with the gallbladder, is employed. A loop of jejunum is selected at a distance of about two feet from the origin of the jejunum so there can be no kink or tension. The loop is brought either over the transverse colon or through the mesocolon and fastened to the gallbladder with a continuous suture of fine chromic catgut (Fig 2). With the thin wall of the gallbladder and only a small opening needed, probably a single rubber band is all that may be necessary, but the three-band technic provides a larger fistula. The band is inserted through the apex of the loop of the bowel, catches a bite of about two centimeters, and then is passed through the gallbladder in the opposite direction (Fig 3). The peritoneum of the bowel is incised and the band is tied very tightly (Figs 4 and 5). The row of sutures of fine chromic catgut is again taken up and continued anteriorly, burying the band (Fig 6). A few interrupted mattress sutures of fine chromic catgut are placed and the ends are left long. A tag of omentum or peritoneum-covered fat is carried around the anastomosis, and the ends of these sutures are passed through the peritoneum-covered fat and tied firmly. At the base of the loop an entero-enterostomy is made by three rubber bands.

We have had two cases of benign obstruction in which this was done, with very satisfactory recovery, and clearing up of the jaundice. Mrs. A. M. R. (Case No. C-433), age 55, was operated upon May 29, 1941. Her icterus index on May 26, 1941, was 55. Mr. E. B. McM. (Case No. C-244), age 64, was operated upon July 17, 1942. His icterus index on July 14, 1942, was 33, and on February 2, it was 8.

In a third case, Miss B R G (Case No B-2607), age 45, had a radical operation for cancer of the right breast on July 28, 1936. Her health seemed good until December, 1941, when she became jaundiced, without pain, and with acholic stools. On January 6, 1942, her icterus index was 131. She was operated upon January 7, 1942. No malignancy was demonstrated, but the gallbladder was enlarged, and there was slight thickening of the head of the pancreas. She had several chills during her convalescence, apparently from cholangitis. She was discharged from the hospital March 14, 1942, improved. Icterus index 28.4. Report April 1, 1942, shows some jaundice still present, and the bowels move several times a day. She has had no chills since July, 1942.

In a fourth case, following dismantling of a previous cholecystoduodenostomy, union to the gallbladder was made with sutures and entero-enterostomy of the jejunal loop with a rubber band. This case is particularly interesting, because it shows the bad result that may follow union of the gallbladder to the duodenum. If there is a benign lesion and the acid contents of the stomach are normal or elevated, sooner or later, the reflux of the gastric contents as ejected from the stomach into the duodenum and the gallbladder causes cholecystitis. Mr L F (Case No A-6273), age 44, had been operated upon elsewhere in November, 1930, for what appeared to be a benign obstruction of the terminal common duct. Cholecystostomy was performed, and the bile drained continuously onto the surface of the abdomen. On March 16, 1931, we anastomosed the gallbladder to the duodenum. He made a satisfactory immediate recovery, and for ten years seemed to be in good health. Finally, however, he had enlargement of the liver and intense jaundice. On November 4, 1941, we disconnected the cholecystoduodenostomy, closed the duodenal wound, united the gallbladder to the apex of a loop of jejunum by sutures, and made an entero-enterostomy in the limbs of the loop by a single rubber band. The liver was much enlarged and showed extensive hepatitis and cholangitis. The gallbladder was hypertrophied and thickened. Obviously, the impulse of the stomach in expelling gastric contents into the duodenum had forced the gastric contents into the gallbladder. For a while the patient did fairly well, but then he developed symptoms of sepsis and died on December 31, 1941. Necropsy showed the liver greatly enlarged, with multiple abscesses and a subdiaphragmatic abscess. The union of the bowel to the gallbladder and at the entero-enterostomy was quite satisfactory, and the communication between the limbs of the jejunum was wide, even though a single rubber band was used. This was one of the earlier cases before using the triple bands.

(1b)—*Obstruction of the Terminal Common Duct when the Gallbladder had been Previously Removed*. We have had three cases of this kind. In one, Mrs J F H (Case No C-755), age 54, the gallbladder containing stones had been removed elsewhere about nine months before her admission to the hospital, with symptoms of common duct stone. She was jaundiced

and the liver was much enlarged Icterus index 27 At operation, on July 18, 1941, the common duct was greatly dilated and five large stones, with some thick, muddy fluid were removed from it A loop of jejunum was anastomosed to the common duct A small rubber band was placed only in the jejunum and the bowel around it was sutured to the incision in the common duct with two rows of fine chromic catgut Omentum was also sutured around the anastomosis An entero-enterostomy was performed between the two limbs of the loop of jejunum by the single rubber band technic The patient made a satisfactory recovery and the icterus index 18 days after operation was 8 April 3, 1943, the bile tract seems to be functioning satisfactorily

In another case, Mrs A P (Case No A-8230) age 62, there was a fistulous tract from the common duct which seemed to discharge all of the bile externally The gallbladder had been removed elsewhere The fistulous tract followed along the outer wall of the duodenum At operation, in September, 1942, a loop of jejunum was opened, sutured securely to the fistulous tract at the level of the duodenum, and a lateral anastomosis with three rubber bands was made between the two limbs of the loop of jejunum The patient made a satisfactory recovery

In the third case, Mrs L W J (Case No C-3247), age 48, there was extensive pancreatitis, hepatitis and cholangitis The diseased and thickened gallbladder had been removed by us four weeks previously The jaundice, however, continued, and there was obstruction at the pylorus by the pancreas Under local anesthesia, on October 20, 1942, a posterior gastro-enterostomy was performed and a loop of jejunum was anastomosed to the dilated common duct The apex of the loop of jejunum was sutured to the undersurface of the common duct with fine chromic catgut A rubber band was passed through the apex of the loop and the dilated common duct and was tied tightly (Fig 7) The suturing was continued around the rubber band This was reinforced by a few interrupted sutures of fine chromic catgut, and peritoneum-covered fat was brought around the union An entero-enterostomy was performed between the limbs of the jejunal loop with the triple rubber band technic (Fig 7) The icterus index which had been 100 gradually came down to 19, and the liver receded somewhat The patient improved for a while, but then gradually sank and died January 24, 1943 Necropsy showed multiple small abscesses in the liver, one of which had ruptured The union of the jejunum to the common duct and of the entero-enterostomy was satisfactory

(2) —*Intestinal Obstruction* We have had five operations of this kind in four patients In some cases of intestinal obstruction, especially when an abdominal operation has preceded the obstruction by months or years, merely severing the obstructing adhesions is sufficient However, in other cases there may have been organic change in the bowel from the compression, so something further is indicated We have had two cases of this type In one, Mr H C M (Case No B-9798), age 47, there was complete obstruction in

the lower part of the ileum resulting from a band of adhesions that seemed to have produced some necrosis of the bowel, though there was no leakage. After dividing the band at operation on May 15, 1941, the necrotic area was protected by folding over and suturing the bowel above and below this area. However, even after dividing the band, a region of probable obstruction was left by the infolding of the bowel. The rubber band technic, using a single band in this instance (our first case), was applied and the patient made a satisfactory recovery. In intestinal obstruction where the wall of the bowel is thin, the single rubber band is probably as satisfactory as the triple rubber band, but if this had been one of the later cases, we would have used the triple rubber bands.

In another case, Mr W B K (Case No C-2873), age 31, the patient had had his appendix removed elsewhere 14 years before being admitted to St Elizabeth's Hospital. There had been episodes of sudden pain in the upper abdomen, which quickly disappeared. The diagnosis was uncertain. While keeping him under observation, there were several of these attacks, all with pain in the upper epigastric region. He finally had a severe continuous attack, with distension and obvious symptoms of obstruction. At operation, on October 6, 1942, a series of constricting adhesions was found extending over the lower ileum. The adhesions seemed to result from the previous appendectomy. After dividing them the lower ileum was found to be thickened and compressed. The triple rubber band technic was used between the dilated loop of ileum just above the constriction and the cecum. The patient made a satisfactory recovery for six days, and then had symptoms of sepsis. He was operated upon again, October 12, 1942, and an abscess in the pelvis was drained. The area of the anastomosis was inspected as carefully and gently as possible, and no evidence of leakage was found. Another ileocolostomy, with rubber band, was performed just above the previous one. A Witzel-type of cecostomy was made, with a small rubber catheter. This was performed because there had developed considerable intestinal distension, apparently from the sepsis in the pelvis, rather than from mechanical obstruction as in the first instance. The catheter came out a few days later and there was no leakage of fecal matter. He recovered satisfactorily.

Another case, Miss A C (Case No C-1267), age 19, had partial obstruction at the terminal duodenum. On February 12, 1942, a duodenojejunostomy was performed with a single rubber band No 32. She made a satisfactory recovery and seemed greatly relieved.

In a fourth case, already referred to, Miss N G N (Case No C-2415), age 62, obstruction followed the application of the rubber bands and an open resection was performed, with recovery. There was a strangulated femoral hernia on the right side and the bowel when released showed a small bruised area. This was infolded with sutures and was by-passed with an entero-enterostomy, with the triple rubber band technic. Obstruction resulted from the combination of these procedures and a resec-

tion was performed on the 4th day after the operation. She recovered satisfactorily.

While it has been apparently proved by Gatch, and others, that there is no specific toxin in intestinal obstruction and that healthy mucosa under normal conditions does not absorb the toxic material in the intestine, it is undoubtedly true that in an obstructed loop of bowel there is a great multiplication of the normal bacterial contents and the *Bacillus aerogenes capsulatus* or a similar Bacterium is usually present. An enterostomy under these conditions is by no means an innocuous procedure, even though the greatest care is taken to wall-off the bowel at the site of the operation. There is a possibility of a slight contamination following along the outer wall of the catheter or tube from the bowel into the abdominal wall. That this is not merely an academic problem has been shown in two experiences of our own. While we have performed hundreds of enterostomies with satisfactory results, in these two cases although there had been no obvious soiling, gas infection developed in the abdominal wall and the patients died. They were given the usual treatment of free incisions, the application of peroxide of hydrogen, and roentgenotherapy.

In recent years the use of the Miller-Abbott tube has helped very much in these cases of distension, but in some cases operation must be performed, and where there is the possibility of a residual partial obstruction, an entero-enterostomy which will by-pass the lesion without opening the bowel should be an excellent procedure. This technic would seem particularly indicated where radical operation cannot be undertaken in cancer of the colon, as in the splenic flexure, though we have had no case of this kind since using the rubber bands.

(3)—*Entero-enterostomy as an Adjuvant to Anterior Gastro-enterostomy or Total Gastrectomy*. This has been undertaken three times. In the one instance of total gastrectomy the entero-enterostomy was made by a single rubber band. M₁ A F D (Case No B-8307), age 54, was operated upon March 11, 1942. He died on March 19, 1942. Necropsy showed that the patient died of pneumonia, but there was a small walled-off abscess around the junction of the jejunum with the esophagus. The entero-enterostomy with a single rubber band appeared in perfect condition. There was no leakage and practically no peritoneal reaction around it, but on opening the anastomosis the rubber band had not cut through and there was no communication.

In another case, M₁s G R N (Case No A-35), age 64, a posterior gastro-enterostomy was performed on September 23, 1941, because there was a large obstructive mass in the pyloric region of the stomach. The posterior gastro-enterostomy did not function. An anterior gastro-enterostomy and entero-enterostomy, with a single band were performed on October 14, 1941. This, too, did not function. Fourteen days after the anterior gastro-enterostomy, a jejunostomy was established lower down for feeding and a mushroom catheter was inserted. The patient who had

been sustained intravenously was in quite a desperate condition. The mushroom catheter pulled out because of too much tension on it where it was sutured to the skin. The patient died from peritonitis the following day. Necropsy showed no definite cause for the failure of the function of either gastro-enterostomy. The stomata were adequate and well placed. The gallbladder contained one large stone and several small ones. The gallbladder was densely adherent to surrounding tissues and to the duodenum. There had been an old perforation of the gallbladder into the duodenum, caused by the large stone, and this had been walled-off by adhesions. The mass was thought to be cancer and inoperable. The entero-enterostomy was found in good condition and 1.5 cm in diameter. There was an error in assuming that the pyloric mass was malignant. Doubtless, if its true nature had been recognized and the proper procedure adopted, the patient would have recovered.

In a third case, M₁ W P M (Case No B-9726), age 53, was operated upon June 19, 1942. An anterior gastro-enterostomy, with entero-enterostomy by a single band, was performed for extensive infiltrating carcinoma of the stomach. He died June 30, 1942. Necropsy showed death due to pulmonary embolism. The entero-enterostomy showed a very small opening.

(4) *The Mikulicz-type of Operation* There are four cases under this head. The triple rubber band technic may be used a short distance below the ends of the bowel (Figs 8, 9, 10 and 11). Drawing the rubber bands tightly during insertion makes the procedure practically aseptic. No fecal matter escapes. A small stoma seems to be established in 48 hours, and it is usually unnecessary to remove the clamps on the ends of the bowel.

In one patient, Mrs G W M (Case No B-7798), age 59, this entero-enterostomy was performed after resection of the cecum and ascending colon on July 24, 1942. The end of the ileum and the stump of the transverse colon were brought up as in a typical Mikulicz procedure. The three rubber bands were inserted, as described. The patient had a bad heart and died seven days after operation from cardiac failure. The bowels had moved normally. Necropsy showed no evidence of sepsis at any point. The clamps on the ends of the bowel were still holding, there was no fecal leakage, and there was a wide opening between the two limbs of the bowel. It seems that the ends of the bowel might have healed solely by the pressure of the clamps.

A rather stout patient, M₁s H K P (Case No B-1821), age 45, had acute symptoms in the lower left abdomen. She was operated upon November 2, 1942, the day following admission. A short segment of sigmoid was found swollen, with its mesosigmoid greatly thickened and edematous. On separating the adhesions of this segment from the parietal peritoneum some pus exuded. It was obvious that a diverticulum had perforated into the mesosigmoid and formed an abscess which had been temporarily walled-off by the parietal peritoneum. The segment of bowel 9.5 cm long, was doubly clamped and resected with the electric cautery, the

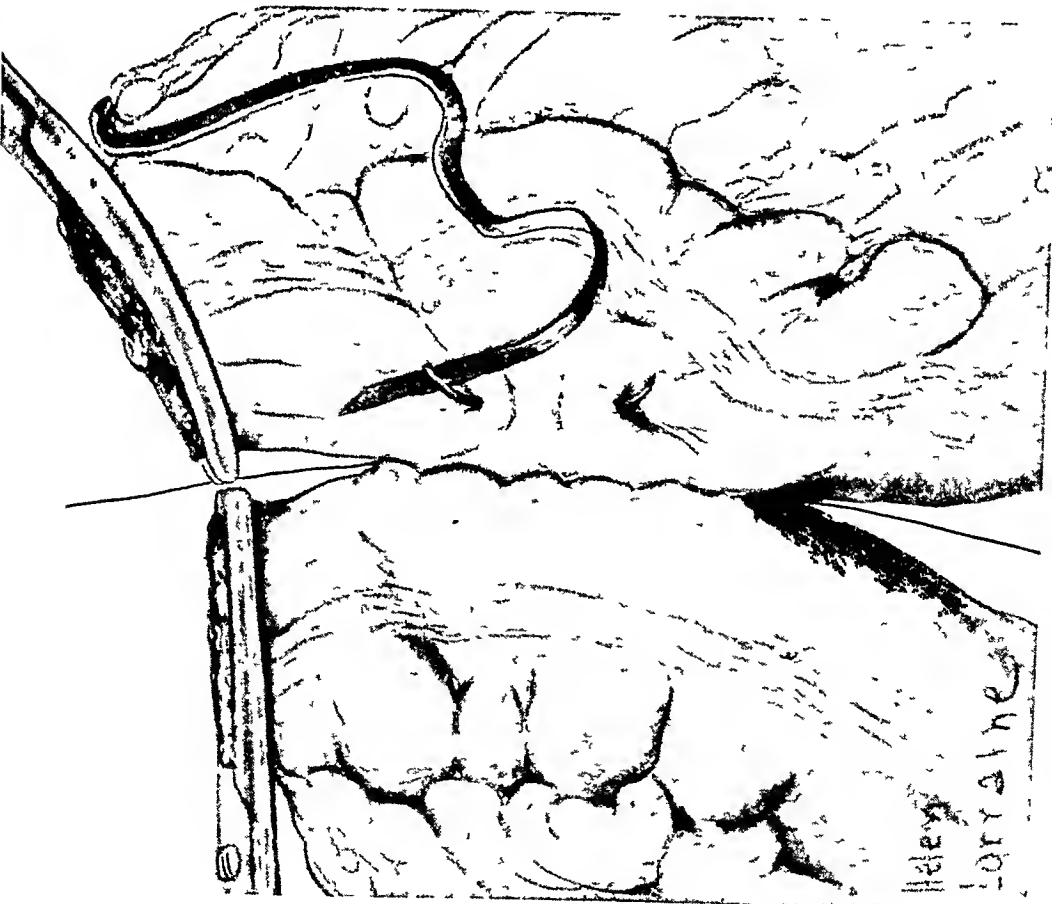


Fig 8—The enteroenterostomy technic is shown as applied in the Mikulicz type of operation. A short distance from their ends the two limbs are sutured together with chromic cutgut. A No. 32 rubber band is passed through first one side and then the other. Note that by puckering the bowel a large bite can be obtained.

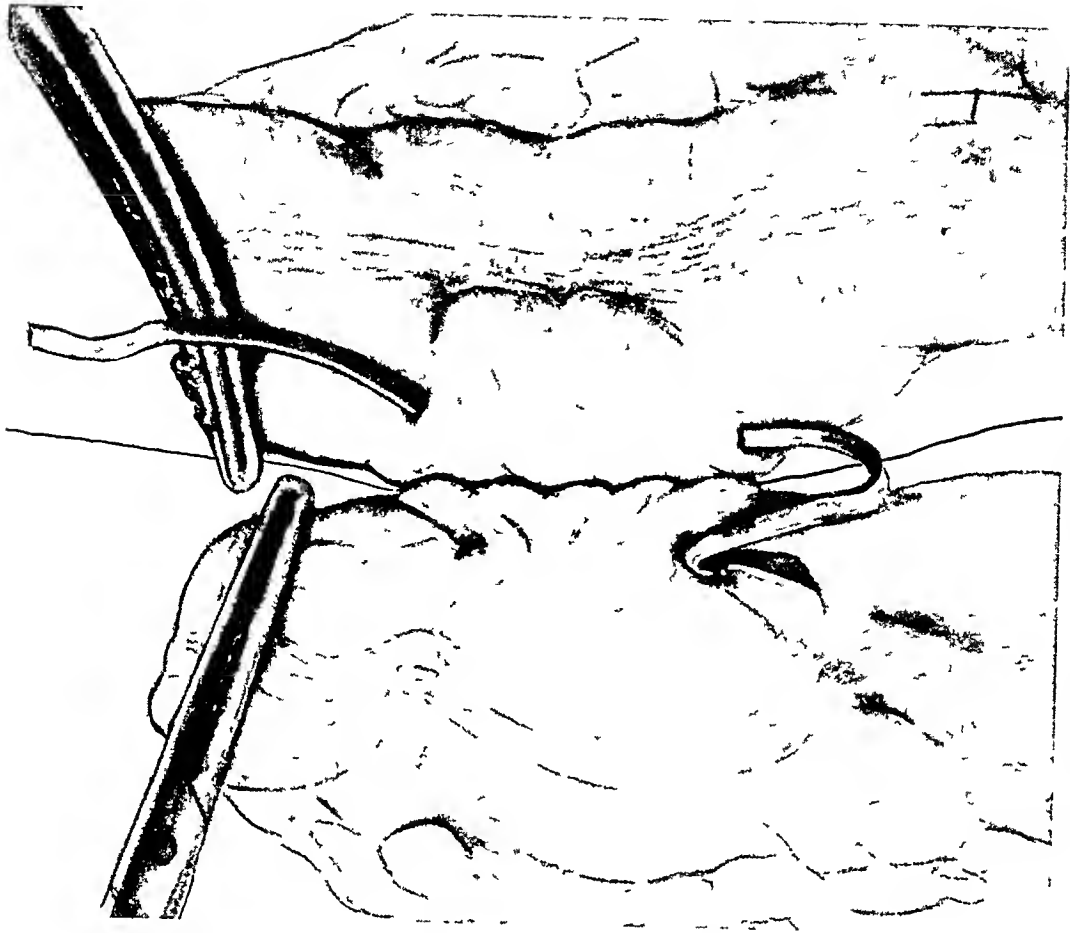


Fig 9—The rubber band is now passed through the left limb of the colon.

two stumps were brought into the abdominal wound as in a Mikulicz procedure, and an entero-enterostomy with the triple rubber band technic was made. The patient had very little discomfort. Seven days after operation there was a bowel movement by anus, and on the same day a small amount of fecal matter leaked from the stump of the bowel. The clamps were removed five days later (12 days after the operation). One end had apparently healed. The anastomotic opening was obstructed by an impaction of fecal matter. This was removed and, with the finger, the opening was located, and two stout rubber bands were passed through this opening

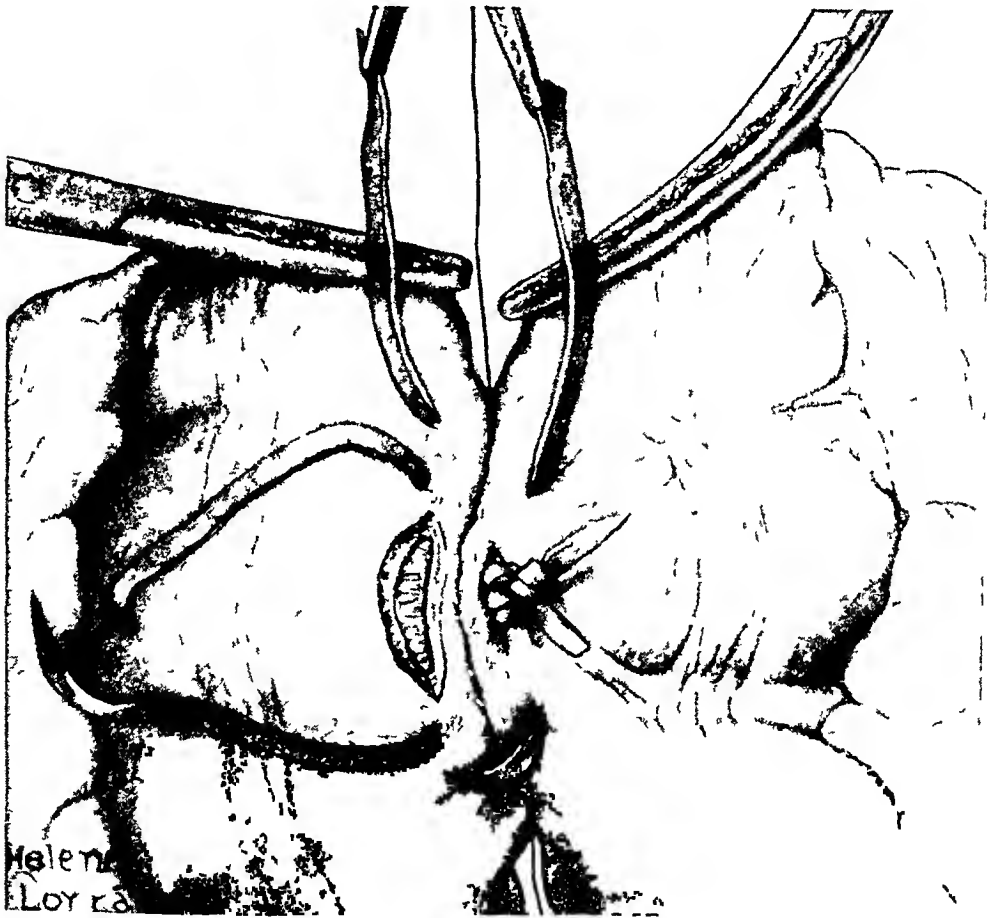


FIG. 10.—The second and third rubber bands have been passed. On the right side the second rubber band has been tied down after an incision through the peritoneum and superficial muscular coat as shown on the left side.

and tied down snugly on the remaining spur. Some sutures brought the ends of the bowel together and the abdominal wound was strapped rather snugly over them. The patient was discharged from the hospital 33 days after operation, with a small fecal fistula which would remain closed for several weeks and then would drain. On April 7, 1943, under local and sodium pentothal anesthesia, the fistula was dissected out and the small opening in the bowel was sutured. She left the hospital the following day. The fistula had caused but little inconvenience. There was no evidence of hernia.

Mrs G A J (Case No C-2592), age 61, entered the hospital, July 19, 1942, with intestinal obstruction from carcinoma of the splenic flexure. On the following day a cecostomy was performed. Nine days later the splenic flexure of the colon (the site of carcinoma and very adherent) was excised, including a small portion of the diaphragm. A Mikulicz operation, with the triple rubber band technic was used. On August 12th two rubber bands were passed through the entero-enterostomy opening and were tied tightly over the spui. The spui, however, continued too prominent and, August 22, 1942, three rubber bands, each on a needle, were passed through the spui, and the ends of the bowel were folded over and sutured. This was followed in a few days by rather profuse fecal discharge and the patient was losing strength so, September 12, 1942, an attempt was made to close the colostomy. It was found that though the spui had been eliminated a portion of a loop of small bowel had been caught with a rubber band inserted on August 22, 1942, and there was a fistulous tract from the small bowel into the colon. This was disconnected, the small bowel was sutured, and the colon closed. The patient's heart condition had been poor and toward the end of the operation the blood pressure dropped and could not be restored. She died a few hours later, apparently of cardiac failure. Necropsy showed the heart about normal size though the muscles were flabby and thin. There was infiltration around the tail of the pancreas and the diaphragm. The opening in the jejunum was about ten inches from its origin. There was no evidence of bleeding and there was practically no blood lost during the operation. The tissue from the region of the resection, however, showed cancer, which had not been removed. The presence of the fistula in the jejunum which was caused by catching a loop of the small bowel with a rubber band in a needle undoubtedly added to the weakness of the patient who was already in poor condition.

Another case, Mr J P W (Case No C-3068), age 66, had been operated upon elsewhere about eight years before admission for carcinoma of the lower sigmoid. A resection was performed. It was a low-grade carcinoma, and he made a satisfactory recovery. Recently he developed a polypoid-like growth in the rectum. Biopsy showed low-grade cancer about grade 15. There was a mass in the abdomen where the resection had been previously done. There were symptoms of occasional obstruction at that point. On December 4, 1942, an abdominal incision was made. The mass consisted of infiltrated bowel at the side of the previous resection. There seemed a possibility of recurrence of the cancer, but at any rate there was obstruction at that point. A Mikulicz type of operation was performed, and the triple rubber band technic was used between the limbs of the sigmoid that were brought together. A posterior linear proctotomy was then performed, and the growth, which was on the left side of the rectum, was excised with the cautery. The segment of sigmoid was not malignant, but made an occasional obstruction. The rectal growth

was a low-grade carcinoma. On the fourth day after operation there was distension of the colon. There was apparently fecal impaction at the site of the entero-enterostomy. The proximal clamp was removed and a catheter was inserted. This relieved the symptoms. Eleven days after the operation two No. 32 rubber bands were passed through the anastomotic opening, which readily admitted the finger, and were tied down snugly on the remaining portion of the spur. A few sutures were placed on the stump of the bowel. After that there was a moderate discharge of fecal matter.

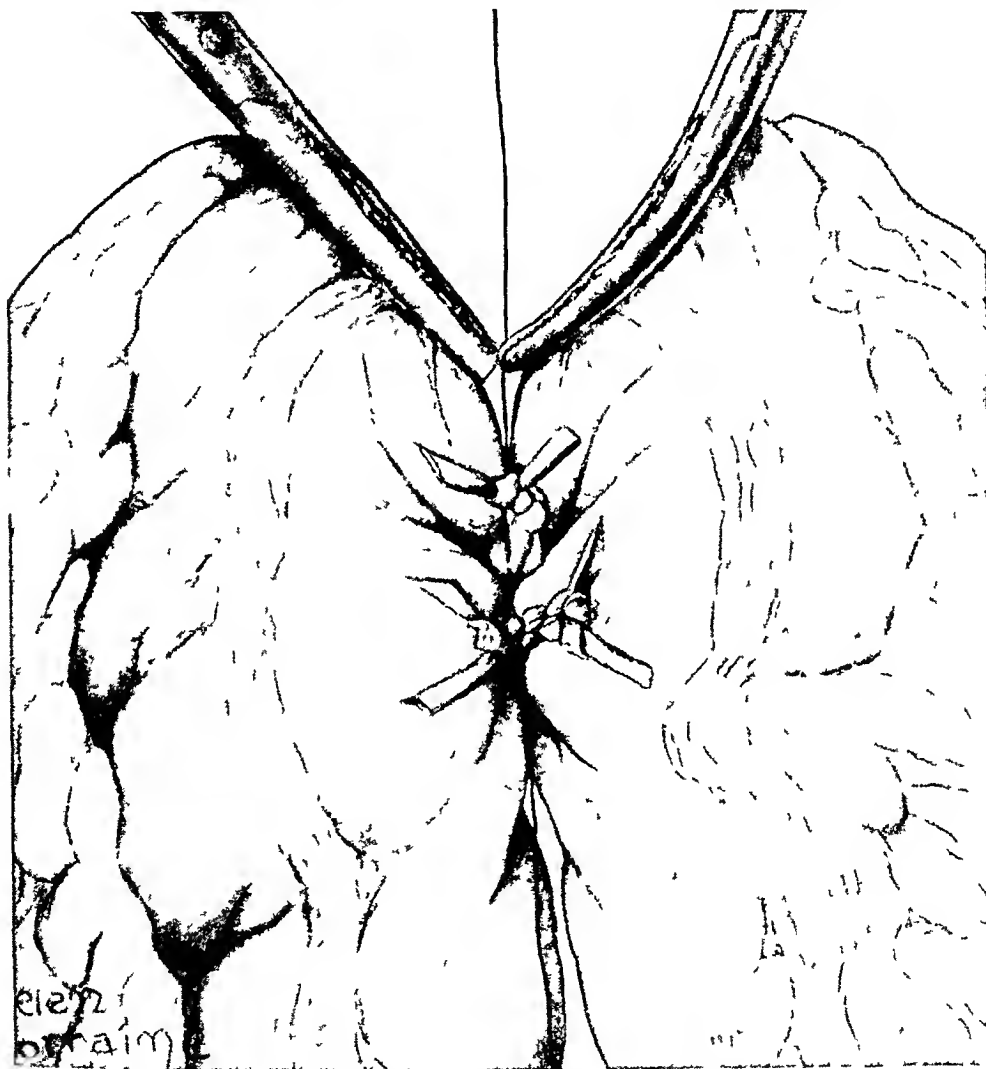


FIG. 11.—The rubber bands have all been tied and the original suture will be taken up and carried forward, burying the knots of the rubber band.

through the fistula, though the bowels moved quite freely through the rectum. However, the abdominal wall was thin and the mucosa everted. It was necessary to close the stoma on March 13, 1942. There was no recurrence of the cancer. He made a satisfactory recovery.

When the clamps are removed a rubber band may be passed down one stump, through the opening made by the rubber band entero-enterostomy and brought up through the other stump tied tightly and the bowel ends

sutured over the band. This completes the division of the spur in a few days.

If the rubber band entero-enterostomy is not performed at the time of the Mikulicz operation, when the clamps are removed a few days afterward a rubber band can be passed through the spur with a needle and tied snugly (Fig. 12). The ends of the bowel are then approximated over the rubber band. There will almost certainly be some fecal leakage for a while, but it will be greatly reduced.

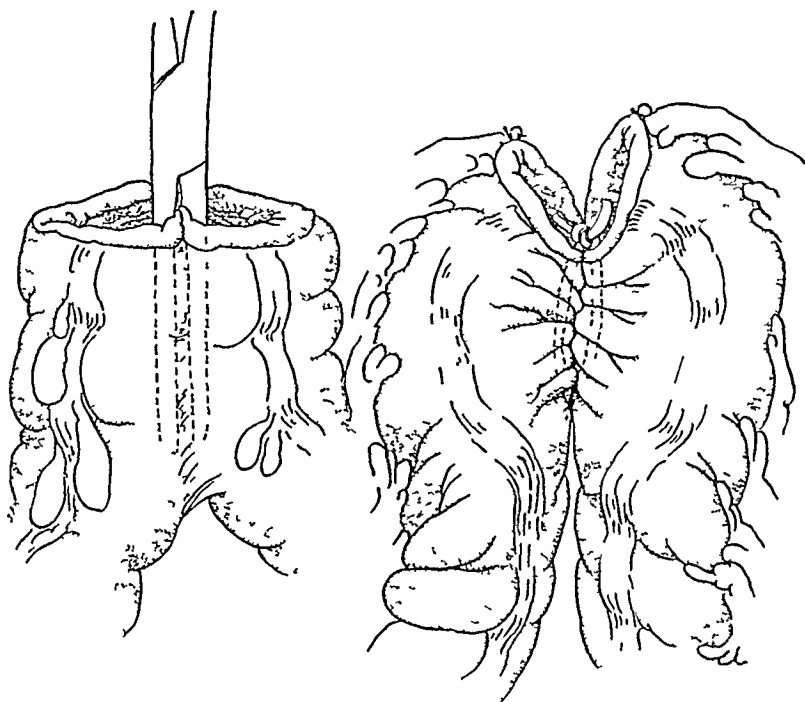


FIG. 12.—The clamps on the ends of the bowel are left on indefinitely. A communication between the two limbs of the anastomosis is doubtless established within two or three days. In one patient, Mrs. G. W. M., who died from a cardiac condition seven days after the operation, the opening was wide, there had been natural bowel movements, and the clamps were still in position with the ends of the bowel apparently healing. Usually, however, there will be some leakage from the stumps of the bowel and when the clamps are removed a rubber band can be passed through the anastomotic opening and tied down tightly on the spur, which completes the elimination of the spur, and the ends of the bowel are sutured over this. There is usually some leakage but it may gradually cease, particularly if the abdominal wall is fat. When however the preliminary entero-enterostomy has not been made, a rubber band can be passed through the spur with a needle from one lumen of the stump to the other and tied down snugly. This drawing shows that such a procedure approximates the ends of the bowel much better than the application of a clamp.

SUMMARY AND CONCLUSION

A closed and practically aseptic method for cholecysto-enterostomy, choledcho-enterostomy and entero-enterostomy with ordinary rubber bands is described. No unusual apparatus or instrument is required.

When this procedure is employed in connection with the Mikulicz type of operation, it simplifies the elimination of the spur and may do away with the necessity of a subsequent formal operation for closing the bowel, which is the chief objection to the Mikulicz operation.

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SOME PHYSIOLOGIC PROBLEMS IN SURGERY OF THE PANCREAS*

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THE OPERATIONS introduced by Whipple, and his associates,¹ for the treatment of carcinoma of the ampulla and by Brunschwig² for carcinoma of the head of the pancreas, result in the removal of the duodenum and portions of the pancreas varying from a small segment to seven-eighths, or more, of the entire organ. In most of the cases the pancreatic ducts are ligated so the patient is deprived of the digestive action of pancreatic juice in the intestines and the pancreas remnant undergoes varying degrees of atrophy. There are, thus, presented to the surgeon many problems that were formerly of concern only to the physiologist. I should like to comment on some of these questions and to indicate, so far as I may, the present status of our knowledge in this field.

IS COMPLETE REMOVAL OF THE DUODENUM COMPATIBLE WITH LIFE?

I first became interested in this problem in 1916, during the course of studies on the cause of death in intestinal obstruction.³ At that time, it was quite generally believed that the duodenum was an organ essential to life in a manner analogous to the adrenal or parathyroid glands. The elaboration of pancreatic secretin by the duodenal mucosa had been well established, and it was thought that either this hormone was necessary or that some other similar substance indispensable to life and the function of the intestines was produced in the duodenum.^{4, 5, 6}

After many unsuccessful attempts, we⁷ were finally able to get a dog to survive the removal of the pyloric portion of the stomach, the entire duodenum, and the upper portion of the jejunum (Fig. 1). While the nutritive state of the animal was not good, the survival demonstrated for the first time that removal of the duodenum was permissible. It is a source of great satisfaction to me to learn from Doctor Whipple that this demonstration, among others, prompted him to undertake the operation for the radical removal of carcinoma in the ampulla of Vater in man. Subsequent experimental studies by Moorhead and Landes,⁸ and Mann and Kawamura,⁹ have confirmed and extended the early findings, and it is now well established that various experimental animals can survive in good health, and for long periods after complete removal of the duodenum provided the

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free flow of bile and pancreatic juice into the upper intestine is not prevented. The absence of the chief source of pancreatic secretia does not preclude, apparently, adequate pancreatic secretion. The susceptibility of these animals to the development of duodenal ulcers⁹ indicates that the buffering action of the duodenal juice is, under normal conditions, of considerable importance in reducing the corrosive action of the gastric juice.

That man can also survive the complete removal of the duodenum is clear from the reports of Whipple,¹⁰ Brunschwig,¹¹ and others. The data



FIG. 1.—The first mammal to survive complete duodenectomy. Operation December 15, 1917, at Iowa City, Iowa. *Am Jour Physiol*, 46, 584, 1918.

at present available, however, do not exclude the possibility that disturbances in hematopoiesis, or other metabolic functions, may appear as late sequelae in man. The demonstration of the role of the stomach in the pathogenesis of pernicious anemia warrants the long continued study of these patients.

II. IS COMPLETE REMOVAL OF THE PANCREAS COMPATIBLE WITH LIFE?

The production of a rapidly fatal diabetes by pancreatectomy in the dog and cat, and its control by the adequate administration of insulin, is so well known that this question is better phrased as follows: Is the complete removal of the pancreas compatible with life when the ensuing diabetes is satisfactorily controlled with insulin?

At the meeting of this association in 1939, I¹² presented a summary of experimental work, conducted in our laboratory for several years, which we interpreted as follows. Confirming the previous findings of Fisher¹³ and

of Allan, Bowie, Macleod, and Robinson,¹⁴ we reported that the depancreatized dog does not survive for long even if the diabetes is controlled by the adequate administration of insulin. At death, a majority of the animals, but not all, display a remarkable accumulation of fat in the liver. The oral administration of from 100 to 200 Gm. of raw pancreas daily suffices to prevent this fatty change in the liver and, if given along with insulin, to permit the depancreatized dog to survive for long periods, or perhaps indefinitely, in a good nutritive state. An experimental analysis led us to conclude that the beneficial effect of pancreas in this connection could not be accounted for by the presence of the pancreatic enzymes, lecithin, choline, or to the general lipotropic action of certain proteins. It was rather due to a specific substance, not present in other organs, such as liver and brain, and the active principle was secured in fat-free, neutral, or alkaline alcohol extracts of beef or pork pancreas. This specific substance was believed to be an internal secretion of the pancreas distinct from insulin and was called "lipocaic" since it seemed to be concerned in a general way with the utilization of fat in the body.

These interpretations were not immediately accepted by all workers in this field, and a considerable effort has been made in my laboratory during the past several years to resolve the various points of conflict. Much of the difference in opinion has been due, I believe, to the fact that attention has been very largely centered on only one aspect of the problem, namely, the extensive accumulation of fat in the liver, and it has been often assumed, but without adequate proof, that the fatty livers which may be produced in normal rats by several different dietary modifications represent the same defect which appears in the insulin-treated depancreatized dog. We have repeatedly called attention to the possible error in such an assumption, and this has become more evident with the discovery that these different types of dietary fatty livers in rats do not all respond to the same kind of treatment. Fatty infiltration in the livers of normal rats may be produced by diets rich in fat, but low in protein,¹⁵ or by the addition of thiamin to diets free from choline but rich in carbohydrates.¹⁶ Apparently, these fatty livers may be prevented by either choline or lipocaic.¹⁷ On the other hand, the type of fatty liver produced by the administration of liver extract or by biotin is prevented by lipocaic but not by choline.¹⁷ Inositol is effective in preventing the biotin type of fatty liver in rats and this fact gave rise to the surmise that the active principle of lipocaic might be inositol. In recent experiments in our laboratory,¹⁸ however, it was found that inositol was entirely ineffective in preventing or curing the fatty livers of depancreatized dogs even when used in doses as large as some of our active preparations of lipocaic. Since these pancreatic extracts could not conceivably be pure inositol it seems clear that the activity of lipocaic is not to be accounted for on the basis of the possible presence of inositol. Proof that the activity of lipocaic is not due to choline was presented in previous reports and conclusive evidence is

now available in the preparation of active pancreas extracts free from choline¹⁹

These findings do not, in my estimation, lessen the significance of the work on choline. It is quite possible, for instance, that lipocaic may bear a relation to choline comparable to that existing between the parathyroid hormone and calcium. Both parathormone and calcium salts relieve the acute manifestations of parathyroid deficiency but the activity of parathormone is not due to its content of calcium. The possibility that lipocaic may play a role in the metabolism of fat through the agency of choline seems worthy of consideration.

McHenry¹⁷ is reluctant to accept lipocaic as an internal secretion partly because the signs and symptoms of lipocaic deficiency do not appear for several weeks after pancreatectomy, whereas evidence of insulin deficiency becomes manifest within 24 hours. This objection seems hardly valid in view of the fact that there is a similar long latent period between removal of the thyroid or the gonads and the appearance of deficiency symptoms. The suggestion of Best, that lipocaic is not an internal secretion but rather a specific dietary factor in pancreas is perhaps a matter of definition. The relief of myxedema or cretinism by the feeding of thyroid extract could also be accounted for by the presence of a specific dietary factor in thyroid but the common view pictures this effect as due to an internal secretion.

I should like to emphasize again that we have been chiefly concerned with the deficiency which appears in the insulin treated depancreatized dog and which, unless controlled, causes death in a relatively short period of time. This deficiency is in part associated with fat metabolism as evidenced by the common appearance of fatty liver, hypolipemia, the aggravating effect of high fat diets and the beneficial action of diets low in fat. Nevertheless, it is quite possible that other and more fundamental deficiencies exist which have complicated and obscured the picture and may be in part responsible for many divergent views.

III. IS THE ATROPHY OF THE PANCREAS WHICH FOLLOWS UPON LIGATION OF THE PANCREATIC DUCTS COMPATIBLE WITH LIFE AND NORMAL NUTRITION?

In the operations for the radical removal of carcinoma of the head of the pancreas, the ampulla, or lower end of the common bile duct the pancreatic ducts are usually ligated and remain permanently obstructed. The pancreas remnant, consisting of the tail and portions of the body, may then be expected to undergo the atrophy so well known in the experimental animal. In the early work, which demonstrated the relation of the pancreas to diabetes, it was found that successful occlusion of the pancreatic ducts in animals caused the acinar tissue to undergo almost complete degeneration and to become replaced with fibrous tissue. The islet tissue on the other hand persisted to a considerable extent and the absence of diabetes in these animals provided the first evidence that it was these structures rather than the acinar tissue that was concerned in carbohydrate metabolism. With the

demonstration that lipocaic as well as insulin is required by the depancreatized dog for survival, it became important to learn if the animal with atrophy of the pancreas following duct ligation might also require lipocaic. The solution to this problem has not only immediate clinical significance but is also important in determining the source of lipocaic and its mode of production.

In one of the first papers on lipocaic from our laboratory²⁰ we reported that three dogs in which the ducts were successfully occluded survived for 44, 56, and 83 days, respectively, and at death extensive degeneration of the pancreas was found. A slight fatty infiltration was present in the liver of two of these animals but the third was normal. These changes were so minimal as compared with the extensive fatty infiltration usually observed after pancreatectomy that the result was considered negative. Since the acinar tissue of the pancreas had very largely disappeared, whereas the islets persisted, it was suggested that these structures were probably the source of lipocaic. In a subsequent paper²¹ the *alpha* cells of the islets were suspected of being the lipocaic organ on the basis of certain indirect evidence and the solubility characteristics of the granules.

In the ensuing years a number of papers dealing with this problem have appeared, some in agreement with our early findings, others sharply divergent. We have, ourselves, continued to work in this field and the added experience has forced us to modify our interpretations somewhat. Before attempting to discuss the work of other investigators I should like to present a summary of our more recent findings. A more complete report will be published elsewhere. Successful occlusion of the pancreatic ducts has been accomplished in 19 additional dogs. These animals were fed meat, whole milk, bread, suet, cane sugar, and Brewer's yeast. Estimations of the blood lipids and sugar were made at frequent intervals, the urine was examined for sugar daily, occasional glucose tolerance tests were made, and at death a careful autopsy was performed, with microscopic examination of the liver and pancreas. The fat in the liver was determined by chemical analysis. The pancreas remnants were examined microscopically and sections, stained by Gomori's method after fixation in Bouin's fluid, were studied to determine the relative abundance of *alpha* and *beta* cells and any remaining acinar tissue.

In all of the 19 animals the pancreas was extensively atrophied at autopsy, and no ducts communicating with the duodenum were found. In ten, the liver fat was within the normal range (three to six per cent), in seven, the fat content ranged from seven to 16 per cent, and in two, the fat was in excess of 25 per cent. Fourteen survived for three months, or longer, and five over six months. Thus of a total of 22 dogs subjected to complete occlusion of the pancreatic ducts, 50 per cent displayed varying degrees of fatty infiltration of the liver, while in an equal number the livers remained normal. It is, thus, necessary for us to conclude that insofar as abnormal fat accumulation in the liver is a reliable criterion of lipocaic deficiency in this situation, a large proportion of dogs, 50 per cent in our series, develop

varying degrees of lipocaic deficiency as a result of the atrophy of the pancreas which follows successful occlusion of the pancreatic ducts

The suggestion has been made that this fatty infiltration is due to the failure of some lipotropic substance (lipocaic) in the pancreatic juice to reach the duodenum²² or to a digestive fault arising from the disturbance in protein digestion in the absence of the pancreatic enzymes¹⁷ If either of these explanations were correct one should expect as high an incidence of fatty livers after duct ligation as occurs after pancreatectomy This is clearly not the case In 154 insulin-treated, depancreatized dogs, reported from our laboratory several years ago,¹⁹ 92 per cent displayed fatty infiltration in the liver attributable to lipocaic deficiency Furthermore, the total deviation of



FIG 2—The photograph on the left illustrates the extensive degeneration of the pancreas three months after occlusion of the pancreatic ducts A fibrous cord represents all that is left The picture on the right shows the normal pancreas and adjacent duodenum

the pancreatic juice from the intestines by means of an external fistula does not produce fatty livers In a recent paper²³ we have reported a series of 17 animals with such fistulae, and in 15 of these the livers remained normal This experiment appears conclusive since the juice was collected quantitatively and subsequent examination failed to reveal any abnormalities in the pancreas

Is there another possible explanation? The view that ligation of the pancreatic ducts produces its effect solely through the removal of the pancreatic secretion has for a long time appeared to me to be not justified by the facts The pancreas undergoes a most extensive atrophy after this procedure (Fig 2), partly due to the pressure of accumulated secretion and partly, no doubt, to interference with the blood supply After some months

all that remains is a thin fibrous cord. It is truly remarkable that this greatly altered organ can still perform a useful function. Microscopically, however, islet cells, identifiable as both *alpha* and *beta* types, may be discerned in a matrix of fibrous tissue and duct epithelium. Acinar cells may be entirely absent after long-standing obstruction, but usually a small number persist for several months. Such a pancreas is no longer an organ of external secretion. Is its function as an endocrine organ unimpaired? The ancient demonstration that occlusion of the ducts does not produce a diabetes comparable to that following removal of the pancreas is not particularly helpful in this connection. A surprisingly small amount of the insulin-producing tissue is adequate to prevent hyperglycemia and glycosuria. Thus, in a recent experiment we performed a partial pancreatectomy in a dog leaving a remnant of pancreas along the lesser duct. Glycosuria and hyperglycemia failed to appear, and glucose tolerance tests remained normal. The pancreas remnant weighed 2.3 Gm., and measured $1 \times 1.5 \times 2.5$ cm. The amount of pancreas originally removed weighed 19.3 Gm. so that in this case the removal of almost nine-tenths of the original pancreas failed to produce any evidence of diabetes. The literature with respect to the influence of ligation of the pancreatic ducts on carbohydrate tolerance is conflicting, some observers reporting an increase in tolerance, others the reverse. I shall not review this data here.

Of the nineteen duct-ligated dogs in our present study, to our surprise a moderate but definite glycosuria developed in seven. The fasting blood sugar was usually normal or somewhat lower than normal values. The ingestion of the standard diet produced a hyperglycemia ranging between 160 and 185 mg. per 100 cc., and glucose appeared in the urine. Glucose tolerance tests displayed the marked hyperglycemia and delayed return to normal characteristic of the diabetic state. There seems no doubt that these animals have become mildly diabetic. Insulin in doses of four to six units daily sufficed to control the glycosuria. When we reflect upon the relatively large proportion of the pancreas which must be removed to produce a comparable diabetes, it is evident that the islets have been extensively damaged.

In a careful study of the cytology of the pancreas of man and the dog by means of special differential stains, Gomori²⁴ has found both *alpha* and *delta* cells outside the islets scattered about in the acinar tissue. *Beta* cells were found only in the islets. In some dogs, Gomori²⁵ has estimated that the number of extra-insular *alpha* cells may actually exceed those in the islets. These observations may prove to be of great significance, for it would seem reasonable to suppose that the *alpha* cells in the acinar tissue would be even more apt to be injured by duct ligation than those in the islets. Assuming, for the moment, that the *alpha* cells are the source of lipocain, an explanation may be seen both for the appearance of fatty livers of varying degrees in duct-ligated dogs and the marked variation in different animals in this respect. With this concept, many of the apparently contradictory findings of different observers may be harmonized. Thus, Boyce and McFetridge²⁶ reported that

ligation of the pancreatic ducts, with pancreas atrophy, does not cause fatty livers but when the ligation is combined with partial pancreatectomy a marked fatty infiltration occurs. In neither case does pancreatic juice reach the duodenum so the variation in result can not be accounted for on that score. It can be explained on the basis of insufficiency of islet function since we should expect this to be greater when partial pancreatectomy is added to the damage due to duct ligation. Person and Glenn²⁷ also observed moderate fatty infiltration of the liver in dogs subjected to duct ligation and partial pancreatectomy. The varying results obtained by other investigators may probably be accounted for depending upon the amount of injury to the islets from the accompanying fibrosis of the pancreas or to the method of duct ligation employed, some workers routinely removing the duodenal portion of the pancreas to prevent regeneration of the ducts.

Additional evidence suggesting that the *alpha* cells are the source of lipocaic has come from a different type of experiment. The repeated injection of extracts of the anterior hypophysis into dogs was found by Young²⁸ to produce a permanent diabetes characterized by degenerative changes in the islets. In a further study of this phenomenon, Ham and Haist²⁹ report that the injection of such hypophyseal extracts produced a depletion of the granules and finally hydropic degeneration of the *beta* cells. The *alpha* cells were unaffected. These dogs had severe permanent diabetes characterized by hyperglycemia, glycosuria, and a very high insulin requirement. They did not have fatty livers. These observations are of course in harmony with the view that the *beta* cells are the source of insulin. Two animals, however, were found in which the *alpha* cells were injured. "In one of these there was a complete lack of *alpha* granules and in the other a moderate degree of *alpha* cell degranulation. The islets in these animals were surrounded by acinar tissue in which the fixation and staining were excellent, hence the lack of *alpha* cell granules could not be attributed to faulty fixation or staining. These two animals, in which *alpha* cells evidenced degranulation, were the only ones in which there was an extensive deposition of fat in the liver." The authors did not interpret their experiments as indicating that the *alpha* cells are the source of lipocaic, but in a personal communication Dr. Ham informed me that this idea occurred to him. In view of the normal appearing acinar tissue it seems safe to conclude that the pancreatic secretion was unchanged and passed as usual into the duodenum. The available data thus point strongly to the conclusion that lipocaic is manufactured by the *alpha* cells of the islets and passes directly into the blood or lymph rather than into the pancreatic secretion.

Adequate data are not yet available to decide whether or no man will require lipocaic after operations which permanently obstruct the pancreatic ducts. That such procedures cause an atrophy of the pancreas resembling that which occurs in the dog is illustrated in Figure 3. In this case pancreatoduodenectomy had been performed for carcinoma of the common bile duct.

and head of the pancreas. Death occurred four months later, and at autopsy the pancreatic ducts were obstructed and dilated. The islets appear to be well preserved and there was no excess fat in the liver. In one of Whipple's patients coming to necropsy nine months after occlusion of the pancreatic ducts, no fatty infiltration in the liver was found.¹⁰ Many of the patients who have survived pancreatoduodenectomy have been given pancreatin, but since this may contain lipocaine the absence of liver fat in such cases has little significance in this problem. Brunschwig¹¹ occluded the pancreatic

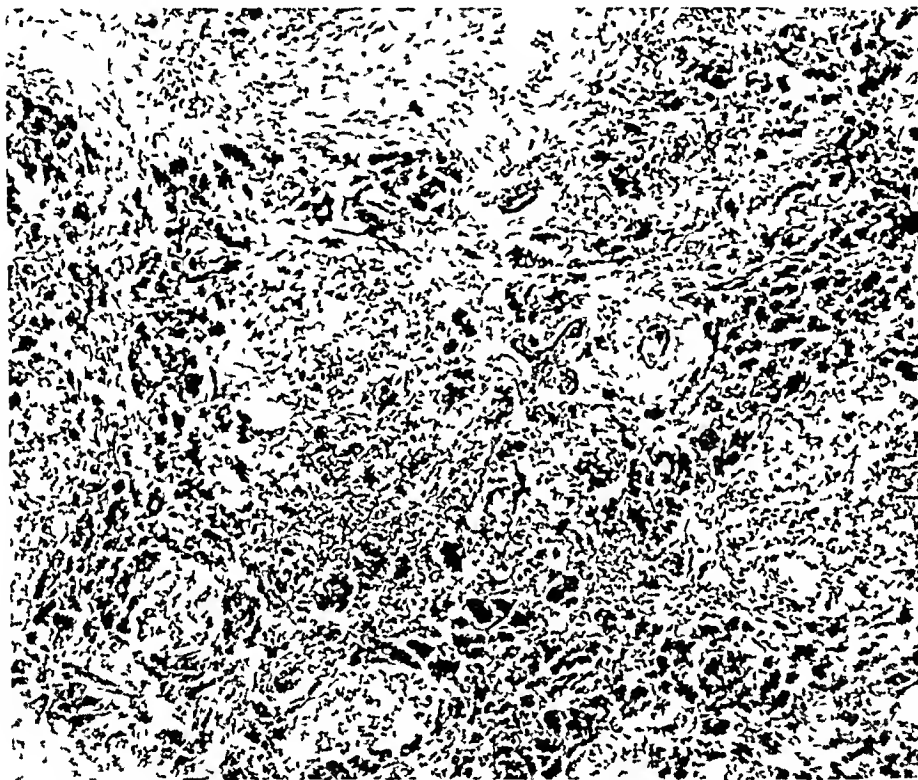


FIG 3—Microscopic section showing marked atrophy of the acinar tissue in human pancreas four months after resection of the head of the pancreas and permanent occlusion of the pancreatic ducts. The acinar tissue is largely but not completely replaced by fibrous tissue. The islets are fairly well preserved.

ducts in several monkeys and did not observe fatty livers in any case. It may be that in man and the monkey the islets are not so greatly injured by duct ligation as in the dog but until much more data become available it appears wise not to rely on such a conclusion. The greater likelihood is that a considerable proportion of these patients will develop both insulin and lipocaine deficiency in the course of time and that these sequelae will be more frequent and severe when, in addition, large portions of the pancreas are removed.

IV WHAT EFFECTS MAY BE EXPECTED TO RESULT FROM THE COMPLETE REMOVAL OF PANCREATIC JUICE FROM THE INTESTINES?

Exclusion of pancreatic juice may be secured by total pancreatectomy, by permanent occlusion of the pancreatic ducts, or by the deviation of the

juice to the exterior by means of an appropriate fistula. Both the local and the systemic effects resulting from these procedures in experimental animals differ widely and these should be kept in mind in a consideration of the clinical problem.

The experiments of Mann,³¹ and Elman,³² have established the fact that diversion of the pancreatic juice from the duodenum into the lower intestine, or the exterior, leads to the production of duodenal ulcers. These have been ascribed to the corrosive action of the gastric juice when its acidity has not been reduced by the sodium bicarbonate of the pancreatic secretion. In my own experience, it has been difficult to prevent the development of ulcers in dogs with total pancreatic fistulae even with the daily administration of large amounts of alkali and I believe that ulcers would occur in almost 100 per cent if treatment were not carried out. What then is the explanation for the almost complete immunity of depancreatized dogs? In a series of over 400 such animals studied in our laboratory duodenal or gastric ulcers have been found less than a dozen times. In both cases the neutralizing effect of pancreatic juice is equally deficient yet in the one duodenal ulcer appears and in the other is absent. The animals with ligated pancreatic ducts occupy middle ground. Thirty-three per cent in our series have developed single or multiple gastric or duodenal ulcers, and several of these have perforated. Pancreatoduodenectomy in man is usually performed for the treatment of carcinoma. It is possible that a partial or complete anacidity may exist in many of these patients and for this reason ulcers may be less apt to develop than in the experimental animal. Even so, it should be remembered that an alteration in the physiology of the upper intestine conducive to the formation of ulcer has been produced and that this can be combated effectively by dietary and alkali therapy.

Although the importance of the pancreatic juice in the digestion of all three classes of foodstuffs has been recognized for many years, there is still uncertainty concerning the extent of the defect which may be expected to appear following the permanent removal of this secretion from the intestines. Most of the studies on this problem have been made upon the dog and the results here have been fairly consistent. Without exception the exclusion of pancreatic juice in this species causes the appearance of large amounts of undigested fat and protein in the feces (Pratt, Lamson and Marks,³³ Ralli, Rubin, and Present³⁴). The severity of the disturbance, however, varied markedly in different animals and also in the same animal from time to time. In a recent study in our laboratory, Vermeulen and Owens³⁵ found that whereas the normal dog absorbed 99 per cent of neutral fat in the diet, after pancreatectomy this was reduced on an average to 47 per cent. Certain animals absorbed only 14 to 33 per cent of the fat, whereas others absorbed as much as 76 per cent. These findings confirmed the previous observations of Pratt.³⁶ The imperfect absorption cannot be accounted for entirely through failure of digestion of the fat since a similar, though less severe, defect was found in the absorption of fatty acids. The normal dog was found to absorb

94 per cent of oleic acid in the diet but after pancreatectomy only 63 per cent. The studies of Whipple, Bauman, and Hamlin,³⁷ and Brunschwig and Allen,³⁸ indicate that a similar disturbance in digestion and absorption, though perhaps less severe, is produced in man. Here again, marked variations were found in different patients, some displaying a very considerable defect while others were practically normal. In this connection, the remarkable ability of the pancreatic juice to find its way back into the intestines after division of the ducts should be kept in mind. This is particularly apt to occur when several anastomoses have been made. While more data on man are clearly needed, it seems probable that most patients will suffer a varying degree of impairment in the digestion and absorption of fat and protein after the operation. This is usually not so severe as to be a serious handicap and does not, of course, forbid the operation, especially since in many patients the ducts have already been obstructed by the disease. The value of substitution therapy is difficult to determine and, here again, the data on man are fortunately more favorable than in the dog. In the latter species the feeding of large amounts of fresh pancreas has been the only method in our experience that has produced a uniform and consistent improvement. Pancreas extracts containing lipocae but no enzymes have been entirely without effect. The defect in absorption is thus apparently not due to lipocae deficiency.

SUMMARY

The discussion of these problems has dealt almost exclusively with data obtained from the experimental animal, which in most cases has been the dog. Certain of the general conclusions derived from such work may probably be safely transferred to man, but species differences must be expected. Pancreatectomy in the monkey for instance produces a less severe diabetic state than in the dog and the same may be true of man. With this reservation in mind, the following impressions derived from work on the lower animal may be suggested as a guide in the clinical problem.

(1) Removal of from 80 to 90 per cent of the pancreas causes no defect in carbohydrate or fat metabolism or in the digestion and absorption of food-stuffs, provided the pancreas remnant remains in connection with the duct and its secretion has free access to the upper intestine.

(2) Removal of from 90 to 95 per cent of the pancreas, leaving the remnant attached to the duct, produces a diabetes, characterized by marked hyperglycemia and glycosuria, excessive insulin requirement, and hyperlipemia. Digestion and absorption are unimpaired. Lipocae is usually required.

(3) Complete pancreatectomy produces, paradoxically, a less severe diabetes, but which is more difficult to control. Hyperglycemia and glycosuria are not so marked and less insulin is required. Hypolipemia develops and lipocae is almost always needed. Moderate to severe impairment in the digestion and absorption of fat and protein may be expected. The absorption of carbohydrate is little affected.

(4) Permanent occlusion of the pancreatic ducts produces a similar impairment in digestion and absorption. Atrophy of the pancreas results. If partial pancreatectomy has also been performed the atrophied remnant of pancreas becomes deficient as an endocrine organ and varying degrees of lipocac deficiency and diabetes appear. Hypolipemia becomes pronounced.

(5) Present information does not indicate that any specific defect will result from removal of the duodenum, but patients who survive for long periods after this operation has been performed should be observed carefully for the possible development of pernicious anemia.

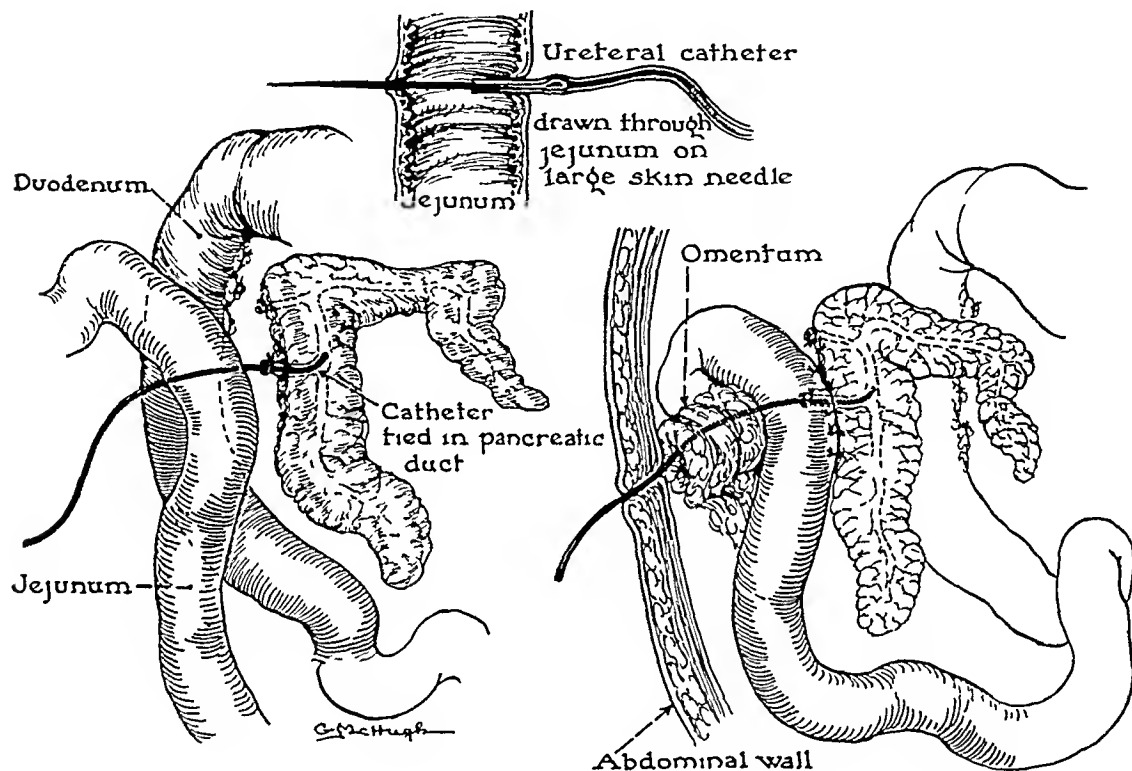


FIG. 4.—Diagrams representing a method for implanting the pancreatic duct into the jejunum which has been found successful in the dog. A ureteral catheter is introduced into the duct and ligated with fine silk. The other end of the catheter is threaded onto a spear pointed obturator or a large skin needle. This is passed through the jejunum and traction on the catheter pulls the pancreatic duct into the jejunum. Omentum is wrapped around the catheter and jejunum and the catheter is led to the exterior by a stab wound. Pancreatic juice drains away as a fistula for five or six days. The catheter is then pulled out and the juice flows into the jejunum. The omentum prevents the formation of a jejunal fistula.

The much better nutritive state displayed by animals in which a remnant of pancreas, however small, is left in connection with its duct, as compared with those in which the ducts are occluded or the entire pancreas removed, suggests that this should be attempted whenever possible. In the treatment of carcinoma of the ampulla or head of the pancreas this will, of course necessitate an implantation of the duct from the pancreas remnant into the stomach or intestines. Methods for accomplishing this have been devised, of which the recent one reported by Person and Glenn²⁷ seems especially promising. In those cases in which the duct to the remnant is dilated or readily

found, the method of implantation illustrated in Figure 4 might be tried. I have found this method satisfactory in the dog and it can be rapidly performed. This is a point of some consequence in a long and trying operation.

Substitution therapy is at present only partially effective. Pancreatin has apparently produced a definite improvement in digestion and absorption in some patients lacking pancreatic juice but in the dog fresh raw pancreas has always yielded the best results. It is probable that most preparations of pancreatin contain some lipocac as well as the pancreatic enzymes, and in large doses might prove adequate. Preparations of lipocac will presumably be made available by the manufacturers when sufficient published reports of its usefulness in man have appeared to satisfy the requirements of federal regulations.

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DISCUSSION—DR ALLEN O WHIPPLE (New York) Doctor Dragstedt always presents work of physiologic significance and his inquiring mind has contributed works of fundamental importance to surgery I have followed his studies on the physiology and pathology of the pancreas with constant interest There are certain points in his paper which I would like to discuss because of their bearings on some recent changes in our operative technic in radical pancreaticoduodenectomy

In 22 experimental animals with duct ligation and atrophy of the acinar tissue, half of them showed no abnormal fat content of the liver and in only two was this fat content in excess of 25 per cent This agrees with our clinical studies in humans

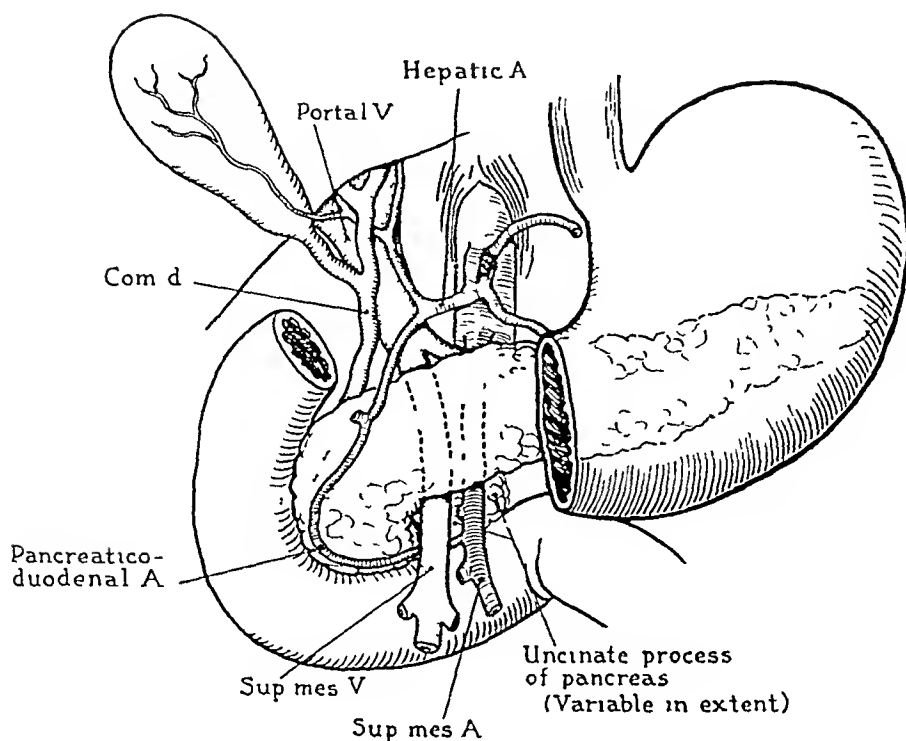


FIG 1—Anatomic points in pancreaticoduodenectomy. Note the importance of the variable extent of the uncinate process in its relation to the superior mesenteric vessels in removing the head of the pancreas.

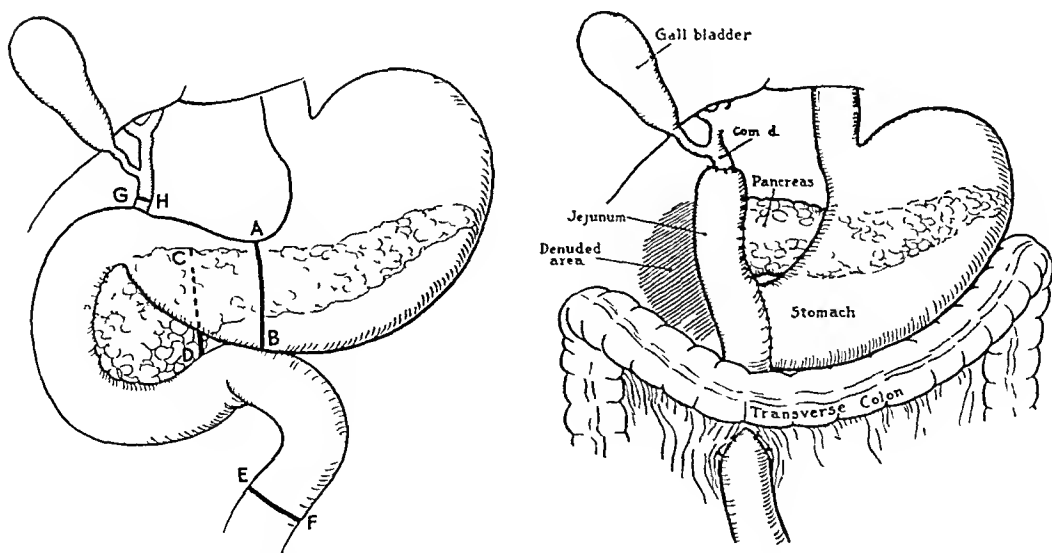


FIG 2—Lines of excision. A B Stomach C D Pancreas G H Common duct E F Jejunum distal to duodenojejunal angle.

FIG 3—The one stage operation, using the distal limb of the jejunum through the rent in the mesocolon for the anastomosis with common duct, pancreatic duct and stomach.

following pancreatic exclusion. In three patients, at intervals of two to 20 months after operation, we found that the patients digested 85 per cent of a measured fat intake. In one patient, however, without the addition of pancreatic extract in the form of haloden, she is able to digest only 40 per cent of a measured fat intake. One of the patients, with an 85 per cent fat digestion, died nine months after operation of a severe cholangitis due to stenosis of the first stage cholecystogastrostomy. The autopsy showed atrophy of the acinar tissue, persistence of islet cells, and no fatty infiltration of the liver. He had not been given any pancreas therapy.

Last week I operated upon a patient for stenosis of a posterior gastro-enterostomy which had been performed three years and eight months previously in a two-stage radical pancreaticoduodenectomy. This man has been actively engaged as a barber in one of the Army camps. After reanastomosing the stomach and jejunum I carefully examined his liver. There was no evidence of carcinoma. His liver looked normal. A biopsy of his liver tissue analyzed for fat showed only 19 per cent of fat. Normal rat livers yield about three per cent. His pancreas showed a fibrosis, with cystic degeneration.

The fact that in both the experimental animal and in patients having pancreas exclusion a certain number will develop impaired carbohydrate metabolism, as shown by varying degrees of a mild diabetes, points to some damage to the internal secretion mechanism both in carbohydrates and in fat metabolism. This is further indicated by the cytologic studies of Gomori, who found *alpha* and *beta* cells outside of the islets. If the *alpha* cells are the source of lipocaic, fibrosis of the excluded pancreas would cause more or less damage to or dysfunction in these *alpha* cells, and would account for the varying disturbance in fat metabolism as shown in the varying amount of fat in the liver following pancreas exclusion. The studies of Ham and Haist in diabetes produced with anterior pituitary extract, as first carried out by Young, would certainly indicate that the *alpha* cells are closely related to lipocaic production.

Because of the variable findings in both experimental animals and in man with the pancreatic juice excluded from the gastro-intestinal tract, it seemed to me that the technic of radical pancreaticoduodenectomy should be changed so as to reestablish the flow of pancreatic juice into the jejunum, in order to improve the existing impaired fat digestion of these patients in whom the flow of pancreatic juice had been blocked for varying intervals, and also to avoid the very annoying complication of a pancreatic fistula which so frequently follows the exclusion operation. The jejunum is considered preferable to the stomach because of the neutralizing effect of gastric juice on pancreatic ferments.

In the last seven of these radical operations I have reestablished the flow of pancreatic juice. In two, this has been accomplished by implantation of the pancreatic stump into the stomach, in two, by implanting the pancreatic fistula into the jejunum at a later operation, and in three I have implanted the pancreatic stump into the jejunal loop which was used for the anastomosis of the common duct and the cut end of the stomach. These two lantern slides illustrate the method of jejunal implantation carried out in the three cases in the one-stage operation. We definitely prefer the one-stage procedure and with the technic as described. This may not be the final answer, but it is a definite improvement in the evolution of the radical operation for carcinoma of the pancreas and ampullary region.

DR EUGENE ROCKLEY (Portland, Ore.) Last June I had the opportunity to operate upon a man who had a carcinoma of the body of the pancreas. I felt that it also involved the head of the pancreas, causing obstruction of the common duct. I, therefore, removed the lower half of the stomach, the entire pancreas, and the duodenum. The fundus of the gallbladder was anastomosed to the jejunum.

Postoperatively, we made the error of administering too much insulin in the first 24 hours, with the result that the man developed an extreme hypoglycemia and had violent convulsions. After that his diabetes was very easily controlled.

He lived 12 days, doing well, eating well, and then on the thirteenth day developed a peritonitis and died on the fifteenth day.

Death was caused by a chemical peritonitis due to a leak at the stump of the common bile duct. It would have been safer to have implanted the common bile duct into the jejunum rather than to have ligated it.

At autopsy, there was found slightly less than one Gm of pancreatic tissue lying between the stump of the common bile duct and the hepatic artery. This patient was not given lipocaine postoperatively. Microscopic study of the liver removed at autopsy showed very little change. There were apparently some fine droplets in the cells, but they did not take a fat stain, so that there was no appreciable liver change in 15 days without pancreatic secretion.

DR ALEXANDER BRUNSCHWIG (Chicago, Ill.) I think Doctor Dragstedt's point is well taken, that technical advances in pancreatic surgery have outstripped advances in knowledge of the physiology of this organ. We can now remove any portion of the pancreas with considerable degree of safety. Total pancreatectomies in man are possible with immediate survival from the effects of operation.

In cases where we remove large portions of the pancreas, with occlusion of the ducts, we are still unable to feel sure that indefinite survival without physiologic disturbance is possible in the face of occluded external pancreatic secretion. Some patients have survived many months without secretion of pancreatic juice into the bowel. Others present bulky fatty stools after pancreatoduodenectomy.

This variability in reaction to the occlusion of pancreatic secretion, that Doctor Dragstedt and Doctor Whipple have commented upon, I think indicates there are some very important factors that are at present unknown in connection with fat absorption and digestion in the bowel.

I present a section from the body of a pancreas in a patient from whom the head and neck of this organ have been removed, and who died five months later of carcinomatosis. Prior to operation there was steatorrhea, and after operation the stool remained bulky and light in color. It does show the persistence of acinar tissue and some proliferation of the ducts. In the animal degeneration of acinar tissue sometimes takes place much more rapidly after duct occlusion than in man.

Another section presented is from a pancreas of another patient operated upon about the same time as the first, by the one-stage resection. The stools, likewise, were fatty before and after operation. The acinar tissue is still present and easily recognizable although fibrosis is more extensive than in the previous sections. This patient survived operation for five months, dying of carcinomatosis. In both of these patients the livers did not show excess fatty infiltration.

There is one point that might be emphasized, and that is the importance of the bile. In dealing with the pancreas, we tend to consider only pancreatic juice. I have observed another patient who presented steatorrhea (6 to 8 light frothy stools a day) for a period of six weeks before operation. At operation, the head of the pancreas was removed together with the duodenum, the lower end of the stomach, and upper two inches of the jejunum, and choledcho-enterostomy was performed. The first stool after operation was more nearly normal than any he had had for several weeks. The stool passed about ten days after operation, and all stools subsequently (patient alive and well one year) were practically normal. In this case, which is an interesting experiment, the one factor returned to the gastro-intestinal tract was bile. Pancreatic juice did not seem to be the factor affecting the character of the stool—since it was absent before (occluded by tumor) and after operation. It was the return of bile that seemed to be the important factor in return of normal stools.

In regard to survival with little pancreatic tissue I simply want to cite an instance of a patient who had a cystadenoma of the pancreas, which grew over the years until it apparently involved almost all the pancreas. Resection of the tumor left about one cubic centimeter of pancreatic tissue. The patient did not have diabetes because of the increased physiologic activity of the minute portion of pancreas left *in situ*. The patient remains well, two years after operation, with no physiologic disturbances and no evidence of hepatomegaly.

DR RICHARD B CATTELL (Boston) Two serious groups of symptoms may be associated with complete interruption of the pancreatic duct. In the first group

the symptoms, due to metabolic changes, result from the loss of pancreatic juices. In the second group, which is no less serious, the symptoms result from the local action of the pancreatic juices on the tissues with which they come in contact. In August, 1939, I performed my first radical resection of the pancreatic head, with a good immediate postoperative recovery except for an external pancreatic fistula, yet the patient died 17 days after operation from secondary hemorrhage from the fistulous tract. The complication of complete external pancreatic fistula is so serious that some such method as Doctor Whipple mentioned today is well worth while.

During the last nine months I have resected the head of the pancreas in seven patients, performing a radical pancreatoduodenectomy. I have attempted to transplant the pancreatic duct or ducts into the jejunum by a relatively simple technical procedure that not only implants the cut end of the pancreatic body but also accomplishes actual anastomosis of the main pancreatic duct. A description of this method appears in *Surgical Clinics of North America*, June, 1943 (Lahey Clinic Number).

When the pancreas is cut across, it is grasped by Allis forceps to control bleeding and to permit visualization of the cut surface. One can see the dilated or normal duct. This is ligated and before release, it is transfixed behind the ligature by a heavy silk suture. Mattress sutures then are used to close the pancreas and to stop bleeding. The loop of jejunum which is brought up for the biliary tract anastomosis is used for the "pancreatic anastomosis." The serosa and muscularis are incised for a distance equal to the width of the pancreas, leaving the mucosa intact. The posterior wall of the pancreas is sutured to the posterior border of the jejunal incision, following which the transfexion suture of the pancreatic duct is passed through the jejunal mucosa and tied down tightly as a necrosing suture. The anterior border of the pancreas then is approximated to the jejunum. The necrosing suture will cut through within 48 to 72 hours.

This method employs the principle of Coffey's third technic of ureteral transplantation, later modified by Lower and Higgins.

By this means we have been able to avoid a pancreatic fistula in some of our patients. In the last nine months I have performed radical pancreatoduodenectomy in a single stage in two patients, and in two stages in five patients, without operative mortality. One patient subsequently died, nine weeks after resection.

DR LESTER R. DRAGSTEDT (closing) I regret that there is not time to discuss all of the many interesting physiologic problems that are raised in surgery of the pancreas, particularly with respect to the influence of pancreatic juice on the digestion and absorption of food stuffs both in man and the lower animals. In experimental work I have been very much impressed with the decidedly better nutritive state of the animal when even a small segment of pancreas is left attached to the duct, as compared with similar animals with extensive resection and in which the ducts are completely obstructed. The preservation of what little pancreas juice is secreted seems to be of great value. Furthermore, the atrophy due to ligation of the ducts is avoided. When, then, extensive resection of the pancreas in man must be undertaken, it would seem wise to implant the stump of pancreas or its duct into the gastro-intestinal tract. We have accomplished this successfully in the dog by a simple procedure that might be effective in man.

THE RECOGNITION AND MANAGEMENT OF ACUTE TRAUMA TO THE PANCREAS WITH PARTICULAR REFERENCE TO THE USE OF THE SERUM AMYLASE TEST*

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THE PANCREAS is protected well by its deep situation within the abdominal cavity. Occasionally, however, it may be injured and, in a patient presenting signs of trauma to the upper portion of the abdomen, the possibility of such injury should be suspected. In some cases there may be no early evidence of damage to the pancreas, in others, signs from trauma to other abdominal viscera are likely to overshadow those arising from the pancreas. No particular group of symptoms or abdominal findings can be considered as diagnostic of injury to this organ. Recently, however, determination of the blood serum amylase has made it possible to recognize many such lesions (some of them only slight or moderate in extent) soon after they have occurred. This determination is made by the well standardized saccharogenic method of Somogyi, and his definition of the unit of blood serum amylase is used. During the last five years 1800 amylase determinations, including those in eight cases of trauma to the pancreas, have been made in the University of California Clinical Biochemistry Laboratory at the San Francisco Hospital. These cases illustrate trauma to the pancreas resulting from penetrating and nonpenetrating injuries to the abdomen and cases in which there was surgical trauma to the pancreas. In each instance of injury to the pancreas in which the determination was made, an elevation of the serum amylase above the maximum normal level (180 Somogyi units) was found at some time after the injury. This increase in the blood serum amylase following trauma to the pancreas probably results from leakage of the enzyme from the injured acini and ducts into the interstitial spaces or into the peritoneal cavity, or both, thence, it is absorbed into the blood.

The case reports that follow illustrate several of the ways in which the pancreas may be injured and the consequent changes in the level of the serum amylase.

In Cases 1 and 2 the pancreas was injured by penetrating wounds of the abdomen.

CASE REPORTS

Case 1—A male, age 37, received a stab wound in the epigastrium, the small opening just inferior to the xiphoid process penetrating into the abdomen. There

* Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

TRAUMA OF PANCREAS

was no abdominal tenderness or spasm. Five hours after injury, and before operation, the blood serum amylase was 241 units (Fig 1). Celiotomy showed a laceration of the transverse mesocolon and a laceration, about 1.5 cm in length, into the parenchyma of the pancreas, with a large hematoma and some necrosis of fat near the head of that organ. The lacerations were repaired and the hematoma was evacuated. A soft-rubber (gutta percha) drain was placed adjacent to the wounded pancreas and brought out through a small stab wound in the right flank.

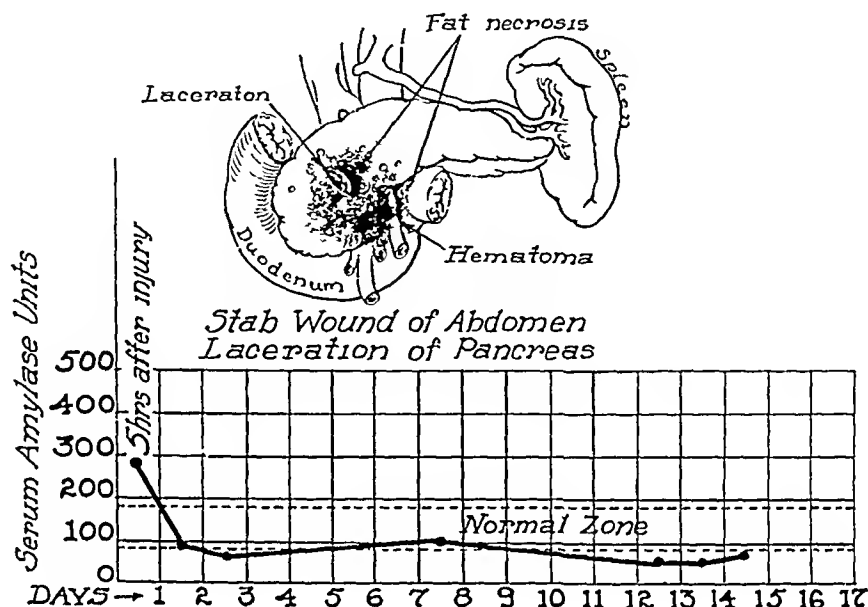


FIG 1—Case 1 Slight rise in serum amylase associated with a stab wound of the pancreas

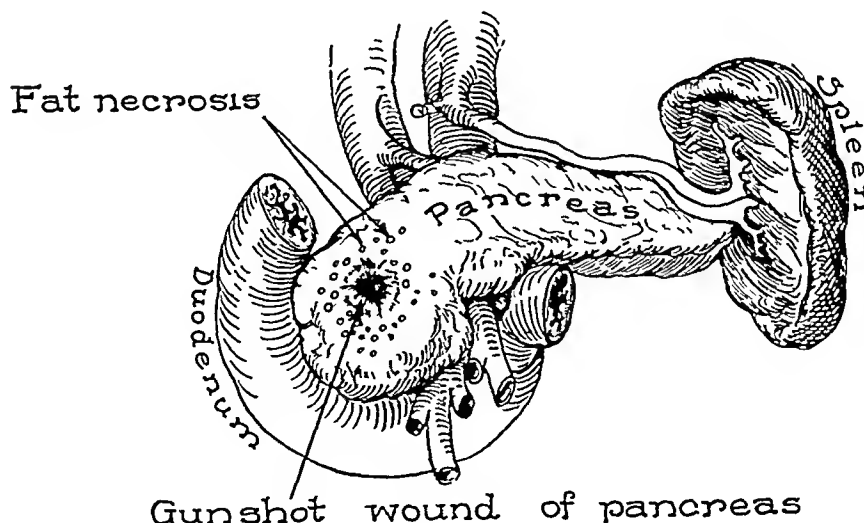


FIG 2—Case 2 Gunshot wound of the pancreas The serum amylase was elevated

Case 2—One hour before his entry to the hospital a boy, age 12, was shot in the epigastrium with a 32-caliber pistol at a range of about 50 feet. He complained of severe abdominal pain and vomited three times. The wound of entrance was immediately beneath the costal margin about one inch to the left of the midline. The abdomen was explored through an upper left rectus incision. A considerable amount of hemorrhagic

fluid was found in the abdominal cavity, and the bullet rested between the coils of the small intestine. Perforations in the anterior and posterior walls of the stomach were closed with sutures. The lesser peritoneal cavity was soiled with gastric contents, and considerable necrosis of fat had occurred in this region. A deep wound was found in the head of the pancreas (Fig 2). The head of the pancreas and the lesser sac were drained by cigarette drains brought out through the left rectus incision. Blood and urine amylase determinations were not made until the ninth postoperative day. A method somewhat different from that used at present was employed, but the results showed marked elevations in the amylase.

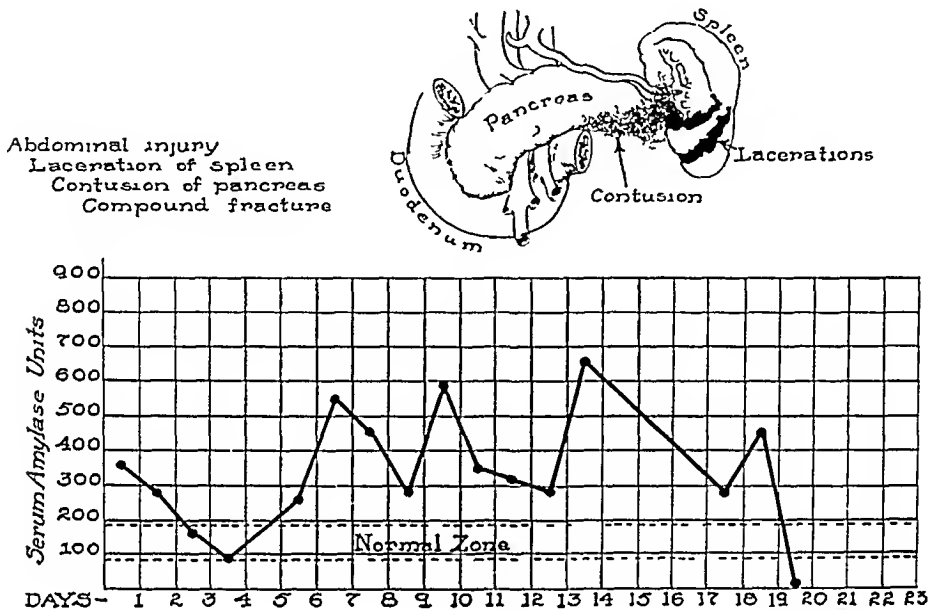


FIG 3—Case 3. Contusion of the pancreas following a nonpenetrating injury to the abdomen produced these elevations in the serum amylase. The readings were increased for the first two days after the injury and then subsided. On the fifth day the serum amylase again increased above normal and remained elevated for about two weeks. This probably indicated a recurrence and continuation of leakage of enzymes from the injured pancreas.

Cases 3 to 7 inclusive illustrate injuries of the pancreas resulting from nonpenetrating trauma to the abdomen.

Case 3—A male, age 35, who had been struck by an automobile, was brought to the hospital with signs of hemorrhage, shock, a compound fracture of the leg and evidence of serious intra-abdominal injuries. The blood serum amylase was 363. After treatment for shock the abdomen was explored through an upper left rectus incision. A large amount of blood was encountered. The spleen was lacerated extensively and the tail of the pancreas was contused and surrounded by hematoma. Splenectomy was performed and the compound fracture was debrided, reduced and immobilized. The abdomen was closed without drainage. Figure 3 shows the serum amylase studies in this case.

Case 4—A male, age nine, was struck by an automobile about two hours before entering the hospital. There were signs of serious intra-abdominal injury with maximum findings in the upper left abdominal quadrant. Before operation the blood serum amylase was 2117 units. A lacerated spleen was removed through a left rectus incision. The abdomen contained 300 cc of bloody fluid. The tail of the pancreas was enlarged and edematous and the surrounding area was infiltrated with blood. Two Penrose drains

TRAUMA OF PANCREAS

were placed and brought out through a stab wound in the left flank. Figure 4 shows the serum amylase readings.*

Case 5—A male, age 32, was injured by a severe blow in the upper portion of the abdomen. Signs indicating serious intra-abdominal injury developed while he was being observed during the subsequent eight hours. The abdomen was explored through an upper left rectus incision. Figure 5 illustrates the findings. A laceration, five centimeters in

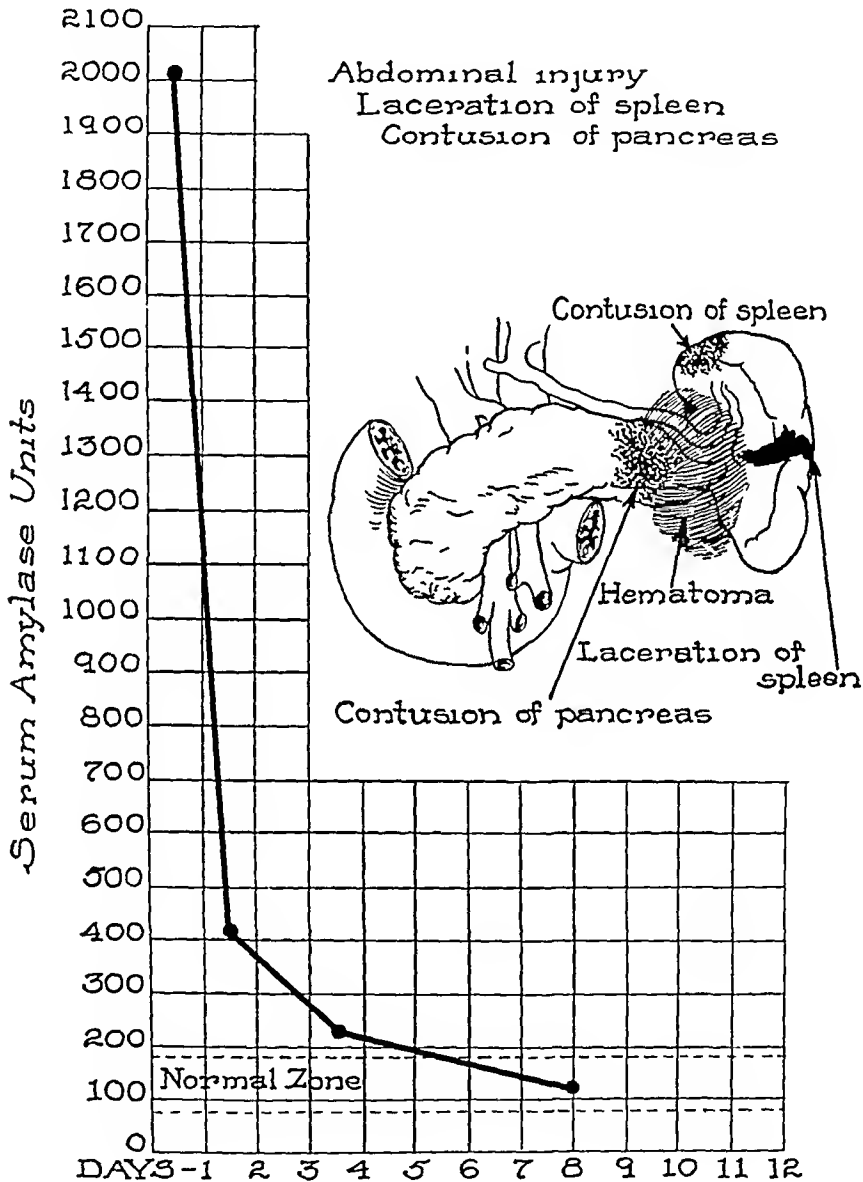


FIG. 4—Case 4. A sharp rise and fall in the serum amylase level was associated with a contusion of the pancreas by nonpenetrating injury to the abdomen.

length, was found in the third portion of the duodenum and was closed with silk sutures. The peritoneal cavity contained bile-stained fluid and the transverse mesocolon was contused and was infiltrated with the same fluid. No determinations were made before operation, but the serum amylase was 282.5 units on the fourth postoperative day.

Case 6—A male, age 42, was injured when the bus in which he was riding capsized. He complained of abdominal pain and signs of shock were present. There

* This case was reported in a previous article on the significance of serum amylase test in the diagnosis of acute pancreatitis.

was widespread contusion of the right upper portion of the abdominal wall. The abdomen became progressively more tender and spastic. Extensive pneumoperitoneum and subcutaneous emphysema were present. The abdomen was explored through a right upper rectus incision. The peritoneal cavity contained blood-stained bile. The first portion of the duodenum and the pyloric end of the stomach were irreparably lacerated and contused. The upper margin of the head of the pancreas was contused. Resection of the lacerated duodenum and stomach was carried out, the duodenal stump was inverted and antecolic gastrojejunostomy was performed. The serum amylase readings are shown in Figure 6.

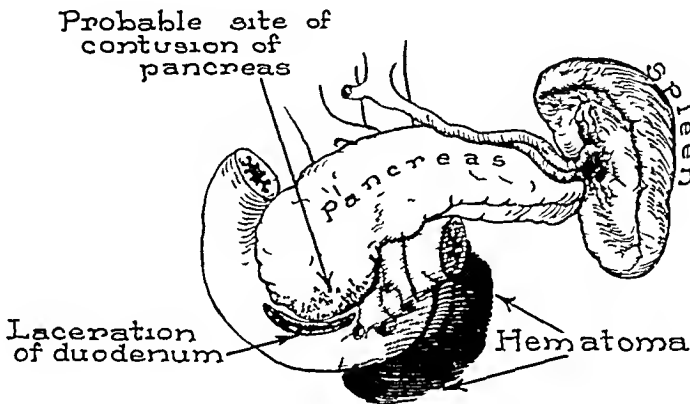


FIG 5—Case 5. An increase in the serum amylase was associated with laceration of the duodenum and contusion of the pancreas in this case of nonpenetrating injury of the abdomen.

Case 7—A female, age 24, fell to the street from a height of about 60 feet. She was in a state of shock. The anterior thoracic wall was deeply contused and a fracture of the forearm and signs of serious intra-abdominal injury were present. She was treated for shock. Celiotomy showed contusion of the left kidney, multiple lacerations and contusions of the spleen and severe contusion of the terminal two inches of the tail of the pancreas (Fig 7). Splenectomy was performed. The serum amylase before operation was 215 units. A few hours after operation it was 633 units and the following day the reading was 523 units.

The serum amylase was found to be elevated in two instances in which operation was performed upon the pancreas (Cases 8 and 9).

Case 8—A male, age 47, complained of epigastric pain and jaundice of two months' duration. Complete obstruction of the biliary tract was present. At celiotomy, a small carcinoma of the head of the pancreas was found. The head of the pancreas with part of the body was resected, the pancreatic duct was ligated and the stump of the remaining pancreas was approximated with sutures. The area was drained. The serum amylase was 310 units following operation (Fig 8).

Case 9—A male, age 53, complained of vomiting and icterus, without pain, of seven weeks' duration. The biliary tract was obstructed completely. A small carcinoma of the head of the pancreas was found at operation, resection of the head and part of the body of the pancreas was performed. The stump of the enlarged pancreatic duct was ligated and the divided end of the pancreas was approximated with sutures. On the day following operation the serum amylase rose to 382 units (Fig 9) but promptly fell again. A pancreatic fistula developed on the ninth postoperative day and, at this time, a reading of 755 units was obtained (Fig 9).

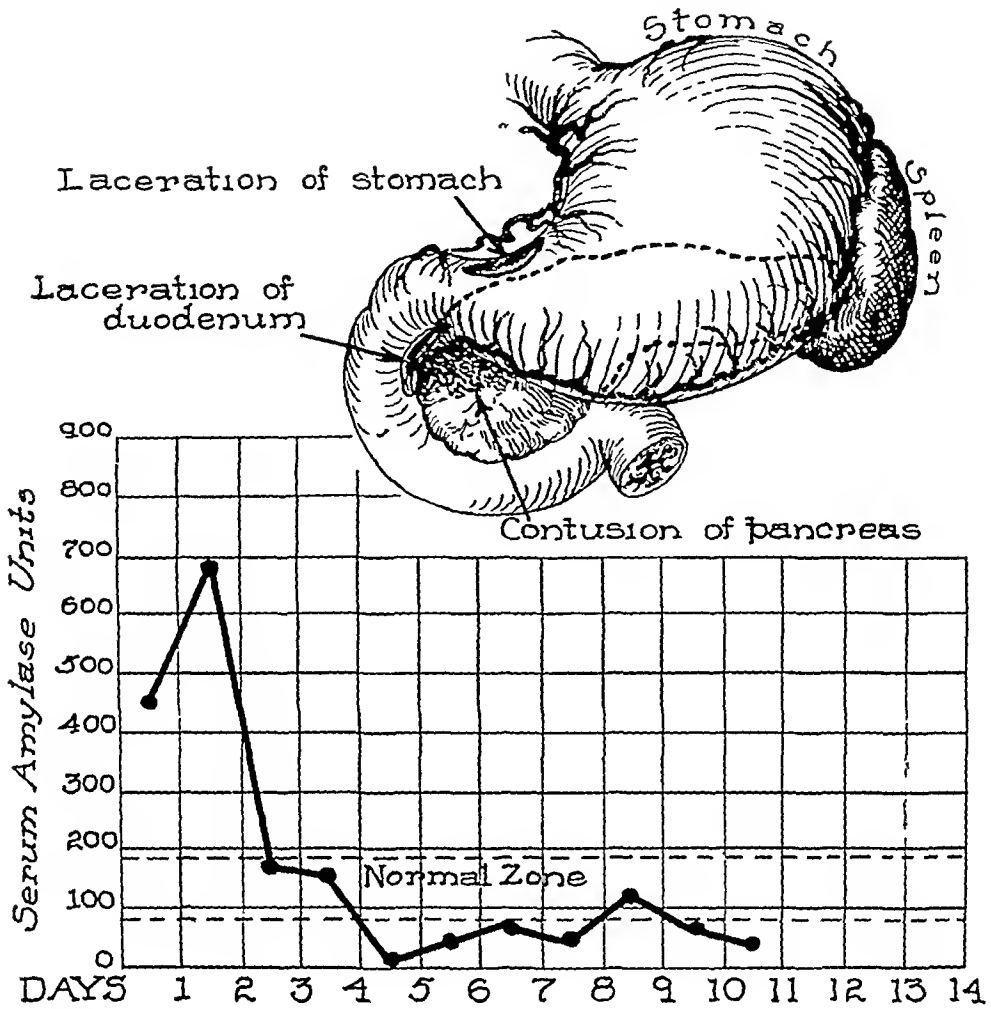


FIG 6—Case 6 A sharp rise and fall of serum amylase was followed by a depression of the amylase below the normal level in a case of contusion of the pancreas caused by a nonpenetrating injury of the abdomen. The duodenum and the stomach were also injured.

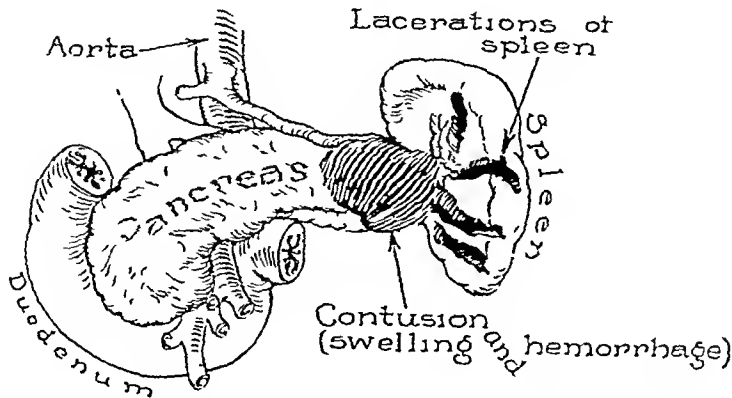


FIG 7—Case 7 An increase in serum amylase was associated with contusion of the tail of the pancreas. The spleen was also lacerated by this nonpenetrating injury to the abdomen.

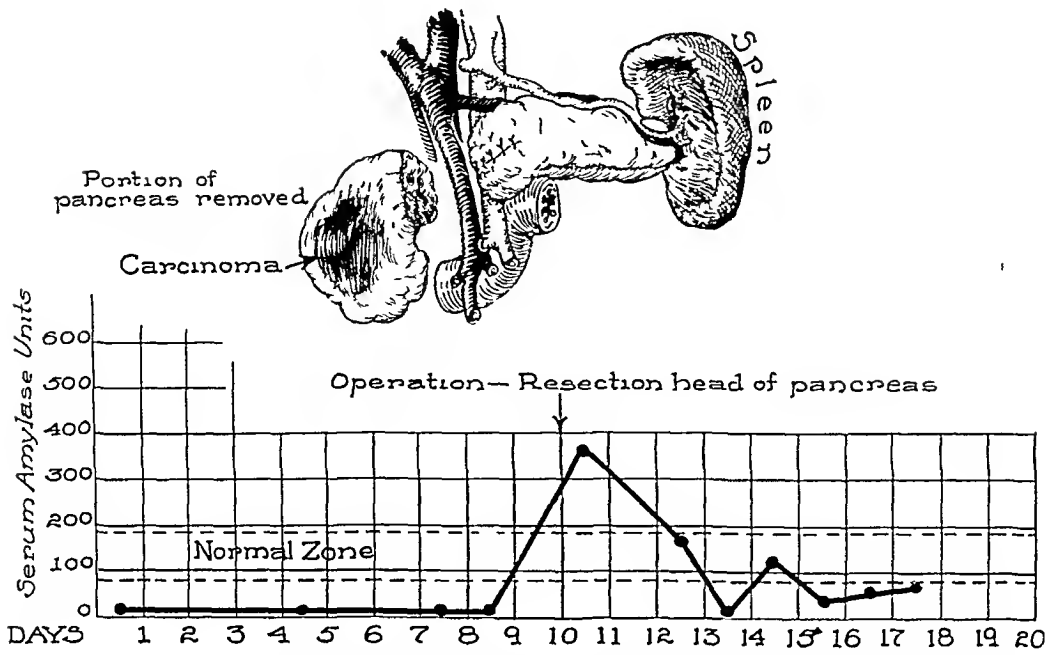


FIG 8—Case 8 Temporary elevation of the serum amylase followed resection of the head of the pancreas for carcinoma

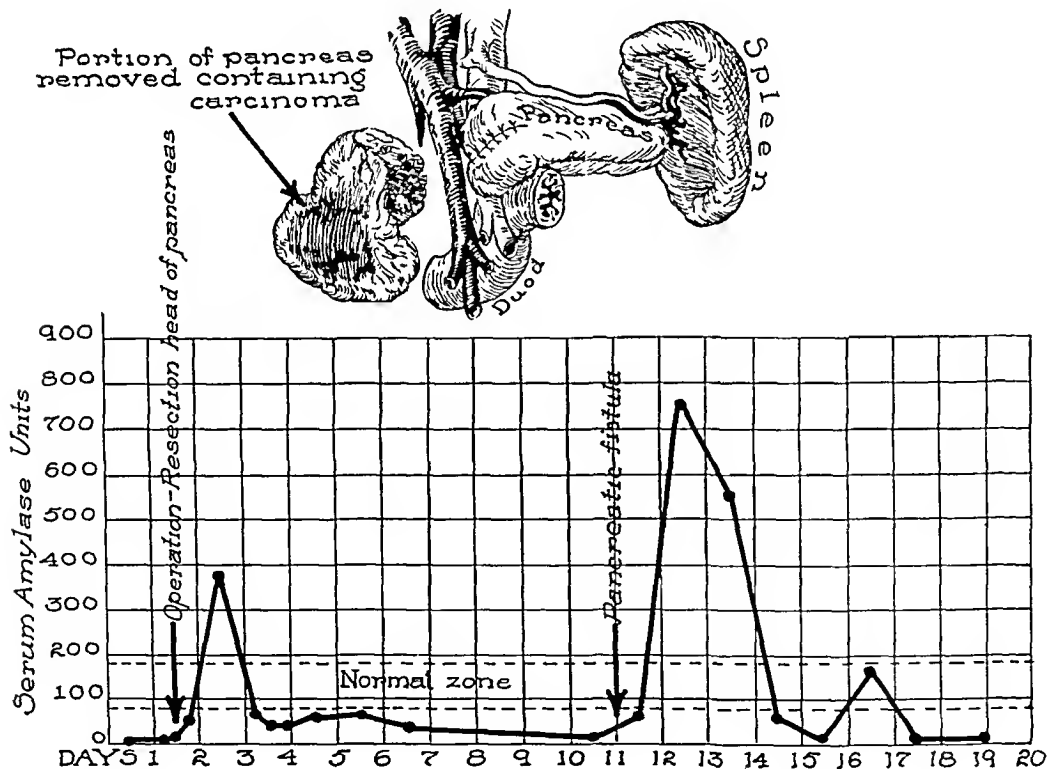


FIG 9—Case 9 A transient rise of serum amylase followed resection of the head of the pancreas for carcinoma. A pancreatic fistula developed on the ninth day after operation and this was associated with a secondary rise in the serum amylase

Rarely, injury to the pancreas may occur during operations for ulcerative diseases of the stomach or duodenum when these organs must be dissected from the pancreas. Also, the pancreas may be traumatized during other difficult operations on the duodenum or lower end of the common duct. No case illustrative of this type of injury is available, however, in which a sufficient number of serial amylase determinations was done to be conclusive.

In a patient who has received an injury to the abdominal region, an elevation in the serum amylase may be considered to be good evidence that the pancreas has been damaged. In most cases there is a rapid rise and fall of the serum amylase following pancreatic injury (Figs 1, 4 and 6), probably corresponding to the period during which enzymes leak from the injured pancreas. Obviously, it is advantageous to be able to detect evidence of trauma to the pancreas before undertaking an operation for serious injury to the abdomen. In such cases an elevated serum amylase indicates to the surgeon that the region of the pancreas should be examined carefully. When objective evidence of intra-abdominal injury is absent or uncertain, an increase in the serum amylase level occasionally may be the earliest sign of injury to the pancreas.

Lacerations of the pancreas, stab wounds and tearing injuries for example, may be closed with nonabsorbable sutures such as silk or cotton. Contused lacerations such as those received with gunshot wounds and contusions from blunt or nonpenetrating injuries usually cannot be closed. Soft rubber-tissue drains should be placed adjacent to the injured pancreas, and often these drains may be brought to the surface of the body through a small separate incision in the flank. The value of drainage in these cases is not established fully but it probably does no harm and possibly is of some efficacy in preventing diffuse peritonitis or the formation of pancreatic pseudocyst following injury to the pancreas. In some cases pancreatic fistula forms as a result of injury to the pancreas. The skin surrounding the drains should be protected well against possible corrosive action of enzymes.

Because feeding stimulates the secretion of pancreatic juice, food should be withheld and supportive measures maintained for several days in cases in which injury to the pancreas is known or suspected. This is particularly desirable if the serum amylase level remains elevated or fluctuates, or if secondary elevations of the serum amylase occur (Figs 3 and 9). It is probably safest to assume that such postoperative alterations in the serum amylase indicate a continuation or a recurrence of leakage of enzymes from the injured pancreas. In patients who show evidence of progressive pancreatic necrosis following injury to the pancreas, drainage of the gallbladder or common duct may be considered, but the efficacy of such a procedure has not been demonstrated. This operation was not performed in any of the cases reported here. Drugs, such as atropine, that inhibit pancreatic secretion were not given in these cases but it is possible that they might be useful.

The significance of elevations in the serum amylase occurring after oper-

ations on the pancreas, stomach, duodenum, or lower end of the common duct is probably the same as that of any other trauma to the pancreas. In such cases the principles governing the surgical and postoperative management are essentially the same as those described for cases of injury to the pancreas from external sources.

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DR. ROBERT ELMAN (St. Louis, Mo.) I would simply like to report, briefly, two observations in confirmation of those of Doctors Naffziger and McCorkle, illustrating the sensitivity and rapidity with which the serum amylase test reflects obstruction or injury to the pancreas.

The first observation was made a number of years ago, while working on pancreatic fistulae, all of the pancreatic juice flowing through a rubber tube to the outside. Many weeks after the operation, when all wounds were healed, the tube was clamped. Within *fifteen minutes* after this obstruction the serum amylase had risen from normal level to about four or five times the normal level and increased to much higher levels afterwards.

The second observation is a clinical one, details of which were furnished to me by Doctor Somogyi. A number of years ago, while studying the amylase content of a great many presumably normal serums, he ran across a specimen that contained a very high level of serum amylase. He found that this specimen was obtained shortly after an abdominal operation and that the amylase value returned to normal the next day. He was interested to know what was found at the operation. He asked the surgeon about the condition of the pancreas. The surgeon said he was sure the pancreas was quite normal because he had palpated and examined it, really vigorously, and, I am sure, massaged the whole organ from head to tail and found nothing abnormal.

TOTAL PANCREATECTOMY FOR CARCINOMA^{*}

CASE REPORT

EUGENE W. ROCKEY, M.D.

PORTLAND, OREGON

INTEREST in the operative removal of tumors of the pancreas has been given much greater impetus in the past fifteen years, particularly since 1935, and the number of reported cases now runs into the hundreds. A search of the literature, however, reveals only two references to so-called total pancreatectomy.

Sauve¹ says in March, 1908, concerning the case of Billroth of 1884

"This case is mentioned in the report of Mayo Robson at the Congress of Paris in 1901. It was probably a question of a total tumor of the pancreas which would have necessitated total ablation of the gland, with recovery.—We have no other indications as to the operative procedure in this case, and we do not take it into consideration."

We have been unable to find any direct report of this case by Billroth.

Sauve also, in the same communication, reports Franke's case of 1900. This report quotes Franke in detail as follows:

"Woman, 68 years old, entered the Clinic on April 30, 1900. Had been operated previously on October 14, 1898, for a tumor of the pylorus, which had caused stenosis. I had done a pylorectomy with gastroduodenal anastomosis by the Koehler procedure. The results were excellent and the patient was dismissed on November 4th. The pancreas had been recognized as healthy, and besides the pyloric tumor was due to an ulcer, not a cancer.

"The patient felt very well after this first intervention until March, 1900. At this period, she became thin, lost her appetite, and noticed a tumor in the operated region. On examination, she was very thin, not recognizable, without a trace of jaundice. The scar was perfect. A little to the right of the medial line, and on this line could be felt a tumor the size of a small apple, scarcely sensitive, slightly movable transversely, much more movable from top to bottom. I thought it a recurrent carcinoma in the scar of the stomach resection, but it was impossible to make a gastric examination, as the patient was vigorously opposed to it. She was easily persuaded to have the operation.

"*Operation* May 1, 1900. Chloroform. Laparotomy above the umbilicus. Duration of the operation one hour and a half. Between the left lobe of the liver, the stomach and the duodenum, were thick adhesions which I had to cut with a thermocautery. The outside of the gastroduodenal anastomosis was so perfect that it almost had the look of a normal pylorus. Behind the stomach was the tumor. The head of the pancreas was invaded by the cancer, the tail appeared healthy, but on thorough examination I discovered that it showed two indurated nodules, and I decided on a total pancreatectomy. The total extirpation was difficult because the compact adhesions joined the pancreas to the retroperitoneal tissues. The adhesions were freed, partly with the thermocautery, partly with the bistoury. The ligation of the large vessels was very difficult; namely, the splenic vein had to be tied twice, numerous ligatures were placed on everything which bled. Under the head of the pancreas I found a small mass the size of a hazel nut, situated against the duodenum. I thought that it was a question of a supernumerary pancreas, and I conserved it. After a careful drying of the peritoneum I closed the wall by layers.

"*Operative Results* Very good. No glycosuria until the fifth day. From the fifth to the nineteenth day a moderate quantity of sugar in the urine (the maximum was 3 Gm. of sugar per litre on the eleventh day).

^{*} Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

"The twenty sixth day the patient left cured, without glycosuria and eating normally. Since then, she has never had any glycosuria. Until July 30, in perfect health, from that time recurrence of the cancer with jaundice and ascites. October 16, died, five and a half months after the operation."

It is to be noted that Franke left a small mass situated against the duodenum, which he thought was possibly a supernumerary pancreas, and that the duodenum was not removed. We feel that in all likelihood a rim of the head of the pancreas adjoining the common duct was not removed, and that it was not a true total pancreatectomy. This opinion would also be substantiated by the very transitory glycosuria that developed postoperatively.

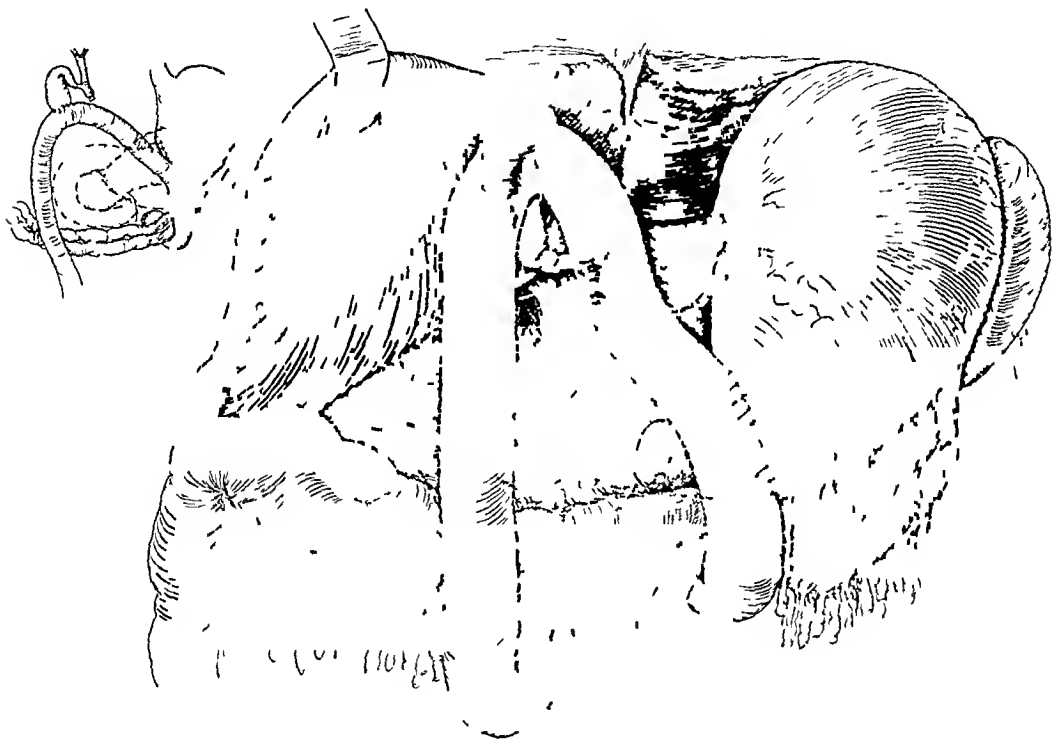


FIG 1—Semidiagrammatic illustration of *en bloc* total pancreatectomy, with total duodenectomy, and partial gastrectomy, with gastrojejunal and cholecystojejunal anastomosis.

Whipple,^{2,3} Hunt,⁴ Brunschwig,⁵ Dragstedt,⁶ Trimble,⁷ and Harvey and Oughterson,⁸ and others, have made important contributions to the technical procedures and problems met in removing the head of the pancreas and the duodenum, together with disposition of the flow.

Case Report—A O., male, age 51. Had been generally well until January, 1942, when he first noted abdominal pain, usually epigastric, but at times in the lower abdomen. There had been a marked weight loss. An appendectomy had been performed elsewhere, without relief of symptoms. There was no change in bowel habit. He gave no history of jaundice. There was an increase in his abdominal distress on eating, and because of this he ate sparingly.

Physical Examination—There was no jaundice. The heart and lungs were normal. Blood pressure 140/90. There was epigastric tenderness, but no muscle spasm. There was a well healed, lower abdominal, right rectus scar. Urine examination was negative.

TOTAL PANCREATECTOMY

for sugar Roentgenograms showed a deformity of both the pyloric end of the stomach and the duodenum This was interpreted as due to both gastric and duodenal ulcers

Operation—June 19, 1942 Median epigastric incision Exploration failed to disclose any gastric or duodenal ulcer There was no carcinoma of the bowel There was, however, a massive carcinoma involving chiefly the body of the pancreas The tumor seemed to extend to the tip of the tail of the pancreas This was rigid and about one inch in diameter The tail was not adherent The body of the pancreas was adherent to the aorta and to the celiac axis The body was the size of a double fist Some of the induration extended irregularly down into the head of the pancreas This apparently was sufficient to cause biliary obstruction, with resultant marked dilatation of the gallbladder

The gastrocolic omentum was divided between clamps and, in addition, the lesser curvature of the stomach was freed, giving good exposure of the growth The gallbladder was markedly distended, and the common duct was dilated, but no stones were palpated either in the duct or gallbladder The problem of total pancreatectomy was considered and discussed As blood for transfusion was not available radical removal was postponed As a palliative procedure an anastomosis was made between the fundus of the gallbladder and the anterior surface of the second portion of the duodenum The abdominal incision was closed without drainage

Three days later a second operation was performed The abdomen was reopened through the upper midline incision The cholecystoduodenostomy was taken down, and a large gauze pack placed in the right lumbar gutter The previously made division of the gastrocolic omentum was extended in both directions The vessels on the lesser curvature of the stomach were ligated and the stomach was divided in its midportion between Payr clamps The entire duodenum was mobilized The opening in the duodenum through which the cholecystoduodenostomy had been done was enlarged and retrograde catheterization of the common duct through the papilla of Vater was attempted The papilla was found to be obstructed The mobilized duodenum was divided just at its junction with the jejunum between clamps The proximal end of the jejunum was closed with three layers of No 00 chromic gut The gastroduodenal artery was ligated and the duodenum together with the head of the pancreas was turned forward and medially The common bile duct was clamped, cut, and ligated with chromic gut The pancreas was freed from the superior mesenteric and the portal veins These structures were adherent, but there was a line of cleavage A pack was placed here The growth apparently extended clear to the pancreatic tail This was freed from the spleen The pancreas was then turned forward and the pancreatic branches of the splenic artery were clamped, cut, and ligated The tumor was not adherent to the aorta, but it was adherent to the celiac axis and to the hepatic artery The tumor was freed from these structures with some difficulty The entire pancreas, lower half of the stomach, and the entire duodenum were removed in one piece An antero-colic isoperistaltic anastomosis was made between the jejunum and the open end of the stomach, with three layers of No 00 chromic gut An antero-colic anastomosis was then made between the jejunum, at a point eight inches distal to the gastrojejunostomy, and the previously made opening in the fundus of the gallbladder A cigarette drain was brought out through a stab wound to the right of the main incision from the region of the stump of the ligated common duct The incision was closed with through-and-through wires and chromic gut, silkworm gut in the skin

The entire procedure took five hours and fifteen minutes During the course of the operation 2200 cc of citrated blood was administered The patient's blood pressure and pulse rate remained the same throughout the entire operation

Pathologic Report—Gross (C H Manlove, MD) "The specimen consisted of tissue from omentum, pyloric part of stomach, duodenum and pancreas The stomach specimen consists of the pyloric and, part, of midgastric region It measures 15 to 17 cm in length from pylorus to proximal cut end The greater curvature reveals several

lymph nodes that vary from 0.5 to 1 cm in diameter. These nodes are firm, and when cut present compact surfaces though the larger surface appears granular. A node is present on lesser curvature near pylorus that is firm, enlarged and was removed for sectioning. The mucosa is reddened and presents usual rugated appearance, and is free from evident changes. The gastric wall shows no evident thickening.

"The duodenal tissue measures 10 cm in length, and the pancreas is attached in usual manner. The wall of the duodenum is without apparent change. The mucosa is intact and the wall soft and pliable.

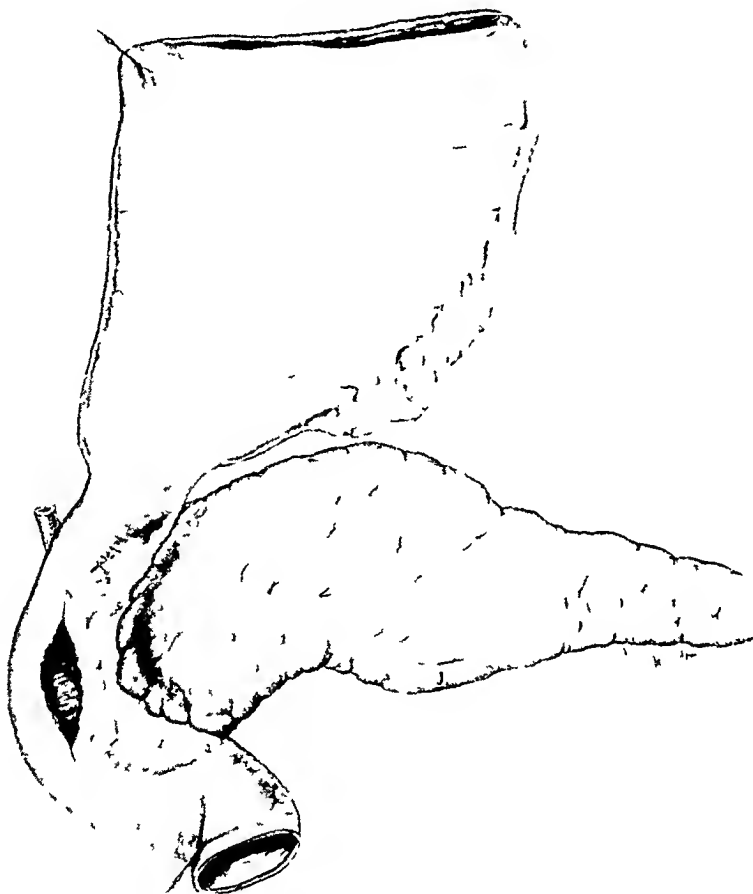


Fig. 2.—Drawing of the operatively removed specimen, the lower half of stomach, and entire duodenum and pancreas.

"The pancreas presents as an elongated rounded structure that measures 17 cm in length. The distal 9 cm is a dense indurated structure which, when cut, is composed of compact gray to yellow colored tissue with thin linear striations diffused throughout. Also, a duct passes through this part of the pancreas. This distal part of the pancreas appears neoplastic while the remaining proximal part presents usual soft, lobulated structural pattern of unchanged pancreas, although in the head near the duodenum, several small gray-white lobules of 2 to 3 mm diameter are seen.

"*Histology*—Sections through distal part of pancreas reveal much of structure composed of fibrous tissue and malignant epithelial neoplasm which replace much of the parenchyma in sections examined. The neoplasm presents as small cords, individual cells, various sized ducts and also seen involving the lining epithelium of ducts. The cells are anaplastic, hyperchromatic and tend in places to goblet cell formation. Here, in this part of the pancreas the neoplastic cells and ducts are closely invested with

TOTAL PANCREATECTOMY

fibrous tissue which varies from a dense to loose formation. At the periphery there occurs areas of gland parenchyma and within these one notes occasional compact mass of cells that may well be Langerhans' islands though no capillary channel is observed. These are noted because in other sections compact cell masses occur that suggest islands of Langerhans as isolated structures and closely invested with fibrous tissue. These are suggestive of regenerative hyperplasia of island cells. In section from midportion these islands are more frequent and in some a capillary bed is present. A large central duct passes through the section. The neoplasm approached the periphery of the section but does not appear in adjacent fat. A small lymph node is free from evidence of neoplasm. *Pathologic Diagnosis: Adenocarcinoma of pancreas.*"

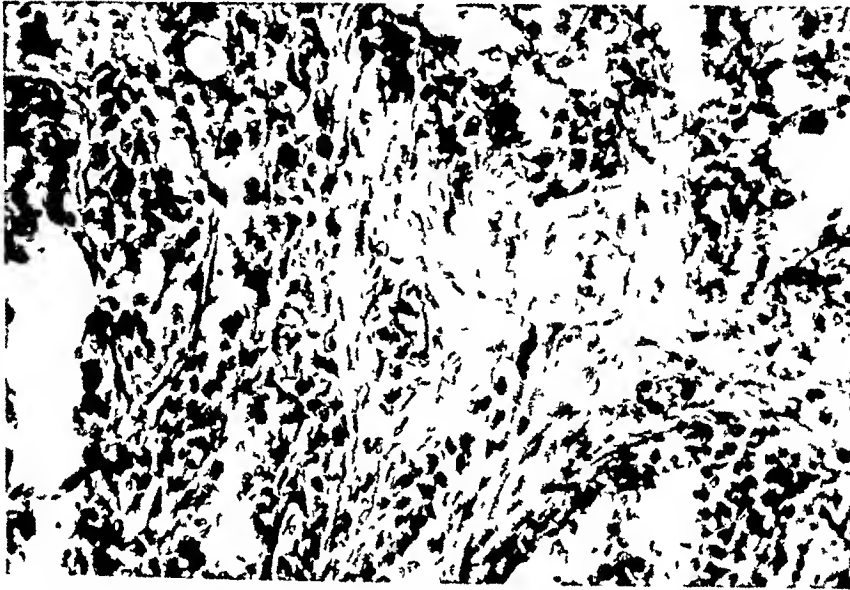


FIG 3—Photomicrograph illustrating the pattern of the carcinoma of the pancreas

Postoperative Course—The patient was in good condition upon completion of the procedure and remained so until the following day when he suffered a severe hypoglycemic reaction with violent convulsions and unconsciousness. This was relieved by administration of concentrated glucose solution. Following this the diabetes was adequately controlled. Intermittent paroxysms of hiccoughs and occasional vomiting occurred during the early postoperative period. Gastric aspiration and inhalation of carbon dioxide 10% in oxygen usually promptly relieved the patient. Fluid balance was maintained by parenteral administration.

On the 10th postoperative day bile seepage from the drainage tract was observed. It was never profuse or irritating to the skin. On the 12th postoperative day he looked well, was eating well, and said he felt well. His abdomen was soft, and his condition was good. The stools were yellow to brown in color. On the 13th postoperative day the patient complained of pain in the left upper quadrant of the abdomen and in the left lower chest on respiration. The findings on physical and roentgenologic examination were those of left lower lobe collapse. On the 14th postoperative day he complained of severe abdominal pain. His abdomen became rigid. His general condition was very poor, and in spite of all supportive treatment he became progressively worse, and on the 15th postoperative day he died.

Study of the postoperative progress of this patient, as outlined in the above summary, indicates that entirely too much insulin was administered on the first day postoperative, resulting in severe and prolonged insulin shock with convulsions. Finally, the operatively produced diabetes was controlled on an average of 27 units of regular insulin daily,

TABLE I

SUMMARY OF POSTOPERATIVE COURSE WITH REFERENCE TO INSULIN DOSAGE GLUCOSE ADMINISTRATION AND DIET

Day of Operation

Total insulin dosage—67 units
 17 units before surgery
 25 units 5 15 P M
 25 units 7 00 P M
 Blood sugar—250 mg at 3 P M
 Glycosuria—3 plus at 4 P M
 Total I V glucose (5%)—1700 cc

1st Postoperative Day

Total insulin dosage—93 units
 Blood sugars— 72 mg fasting
 40 mg 12 M
 40 mg 5 P M
 212 mg 7 15 P M

} Severe and prolonged insulin reactions

Glycosuria—none in 24 hour specimen for this day

Total I V glucose—2000 cc (5%)
 50 cc (50%)—this was given in 2 injections 25 cc at 12 45 P M and 25cc at 3 00 P M

2nd Postoperative Day

Total insulin dosage—12 units
 Blood sugar—80 mg fasting
 Glycosuria—23 gm in 24 hour specimen for this day
 Total I V glucose—2000 cc (5%)
 10 cc (50%)
 Total I V saline—1000 cc

3rd to 14th Postoperative Day

Insulin dosage raised to high of 27 units
 Glycosuria—0 to 24 gm (24 hour)
 Blood sugars—200 to 286 mg
 Alkali reserve—45—(14th p o day)
 Feedings—C- P- F-
 100 60 60 throughout this period

No evidence of ketonuria at any time during postoperative period

which is far less than would be anticipated from the experience gained in treating patients with diabetes

The explanation of the low insulin requirement in this patient is obscure. The lesson to be learned from the experience in this case is, as far as insulin dosage is concerned, that insulin dosage should be more accurately controlled by blood sugar determinations, and that hypoglycemia should not be produced.

Postmortem Examination—Dr C H Manlove. The body was slightly icteric. The operative wound was well healed except in its upper portion. About 500 cc of clear yellow fluid was present in the left pleural cavity. There was almost complete atelectasis of the left lower lobe. No obstructing mucus could be demonstrated.

The abdominal cavity contained a very large amount of serofibrinous, bile-stained exudate. This exudate was found between all loops of the bowel, and had produced adhesions between these loops, and between other parts of the intestine and the abdominal wall. The pyloric end of the stomach, the duodenum, and the pancreas had been removed by surgical operative procedure *in toto*. The closed end of the first portion of the jejunum was buried in the region of the ligament of Treitz. The anastomoses between the jejunum and the stomach and gallbladder were in good condition. When these structures were ballooned out with formalin no leakage occurred. The ligated end of the common duct was not identified, apparently it was open.

The former bed of the pancreas showed a moderate inflammatory reaction and some exudate and disintegrated tissue consistent with the removal of this organ and the elapsed time.

TOTAL PANCREATECTOMY

The liver weighed approximately 1400 Gm. The surfaces made by sectioning appeared very dark brown, compact, and glistening. The bile ducts were not enlarged. The portal vein was widely patent. The splenic vein was not observed.

The small and large intestine were not unusual. A small amount of fecal material was present in the colon.

The spleen was adherent to the parietes and was coated with a serofibrinous exudate. Two irregular pale brownish areas, one somewhat round, the other elongated, measuring about $4 \times 3 \times 2$ cm, were found in the spleen. These had the appearance of infarction.

The adrenals showed no changes. The kidneys were very soft, but were otherwise not unusual. The central nervous system was not examined.

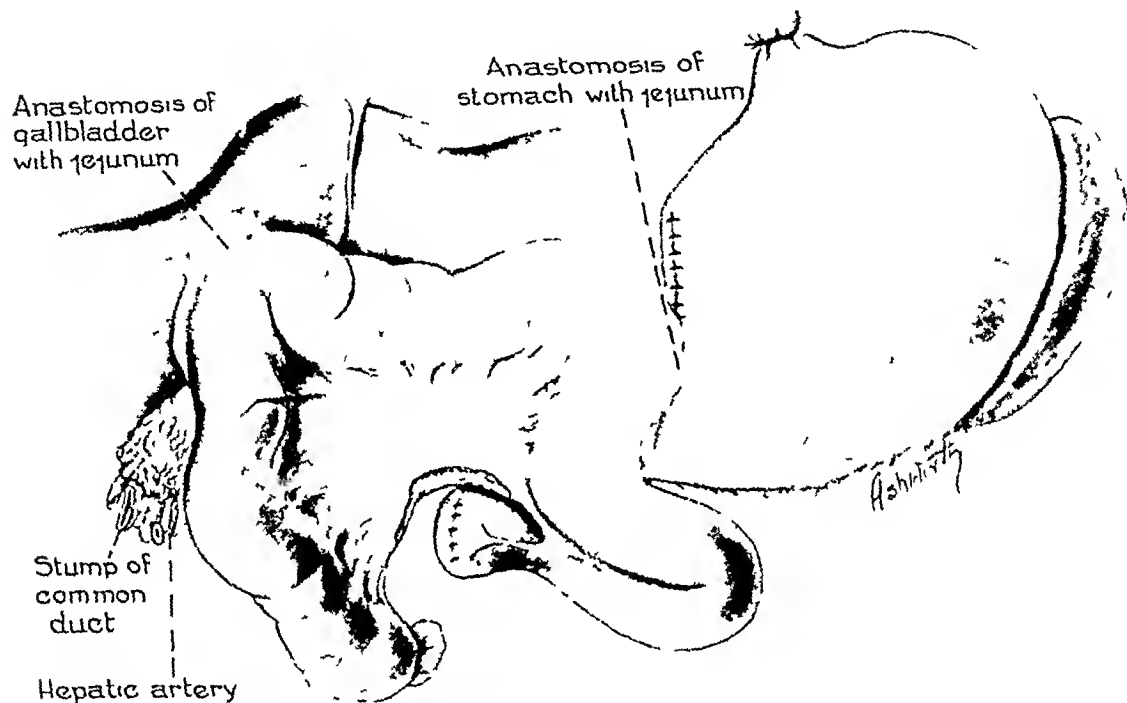


FIG 4—Drawing of the autopsy specimen. The hepatic artery had been divided postmortem.

Careful search and dissection of the postmortem specimen failed to disclose any residual carcinoma. There was found pancreatic tissue lying just between the stump of the common bile duct and the hepatic artery. This weighed slightly less than one Gm (Figs 4 and 5).

Microscopic sections of the liver reveal no striking alteration in structure that may be seen in the "hepatic trinites," or within the parenchyma itself (Fig 6). There are no evidences of marked liver damage. Some of the liver cells appear to contain fine droplets which, however, do not stain with Sudan III. There is some dissociation in the liver cord cells which may be due to postmortem changes.

In summary, it may be pointed out that there existed a carcinoma in the distal part of the pancreas in association with distinctive fibrosis, the cause of which is not clear. If the carcinoma was superimposed upon an interstitial fibrosis and pancreatitis, it must be assumed that that had an unusual distribution, as it involved the body and tail of the pancreas without causing marked alteration in the head. It would, therefore, appear that the carcinoma and fibrous pancreatitis are included in one entity. The surgical removal of the pancreas, together with the portion of the stomach and duodenum, and the union of the gallbladder with the jejunum has not resulted in histologic evidence of liver damage or bile retention. *Cause of Death* Carcinoma of pancreas (removed), chemical peritonitis (bile), atelectasis of lung.

Pierson⁹ has recently carried on an investigation of the blood supply of the pancreas in the Department of Anatomy, University of Oregon Medical School. This comprises 50 dissections. He shows (personal communica-

FIG 5

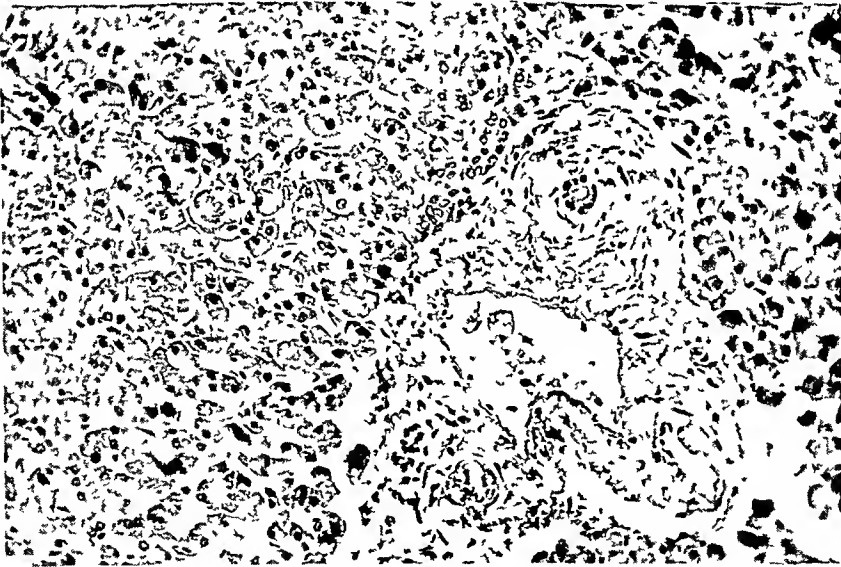
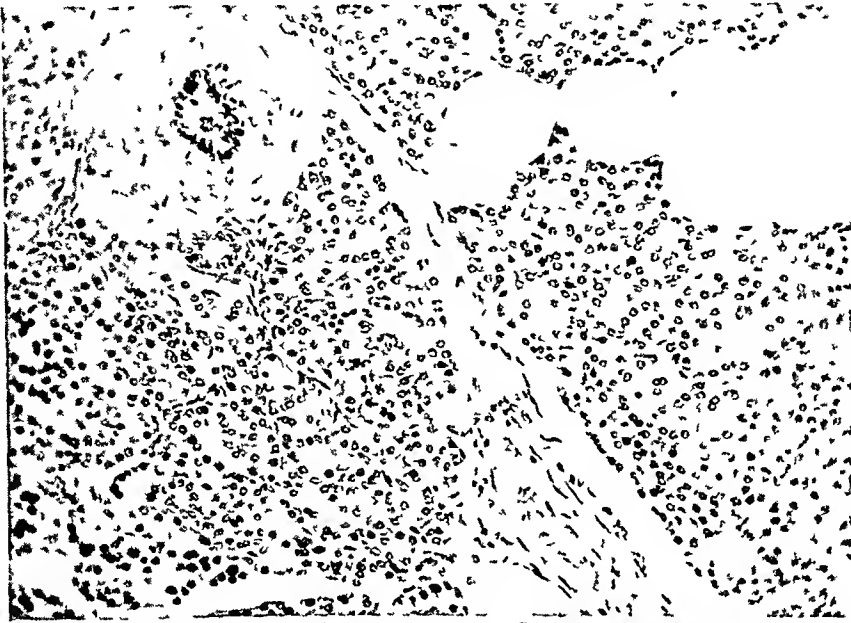


FIG 6

FIG 5—Photomicrograph illustrating the pattern of the pancreas in the small portion remaining near the ligated stump of the common bile duct. It weighed slightly less than one Gm. This pattern also prevailed in the proximal part of the operatively removed pancreas.

FIG 6—Photomicrograph illustrating the appearance of the apparently intact functioning liver structure, after the operation mentioned above.

tion) that as the posterior superior pancreaticoduodenal artery crosses the common bile duct it gives off small branches to it, and that these course upward from its inferior end.

COMMENT —Had there not been the leakage of the stump of the common bile duct, and the attendant chemical peritonitis, the likelihood is that this man would have survived. The anatomic studies of Pierson show that the common bile duct usually gets its blood supply from below. As has been pointed out by both Whipple and Trimble, implantation of the common duct into the jejunum is probably a safer and wiser procedure. This would tend to give the stump of the duct additional blood supply from the jejunal host.

There were no fatty changes in the liver in the two weeks' period of time.

The insulin requirement did not reach the anticipated level. Frequent blood sugar determinations are essential to avoid hypoglycemia.

SUMMARY

A case of carcinoma of the pancreas, with total pancreatectomy has been described. Death occurred 15 days later from chemical peritonitis (bile). Suggestions for similar cases have been made.

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EXPERIMENTAL STUDIES ON PERITONEAL ADHESIONS FOURTH REPORT—SULFONAMIDES WITH AND WITHOUT HEPARIN*

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THE PROVEN EFFECTIVENESS of the sulfonamides in controlling certain phases of infection has led to a widespread use of these drugs within the peritoneal cavity in the presence of contamination or infection^{2, 3, 4, 10, 11, 12, 13, 14} However, the literature on the relationship of the sulfonamides to the formation of peritoneal adhesions is scanty In addition to casual references in various articles, a few specific comments may be found For instance, Throckmorton¹³ concluded from experimental work that sulfanilamide and sulfathiazole do not create adhesions in the rat Jackson³ found "no evidence of untoward irritation" when sulfanilamide was introduced into the normal peritoneal cavity of the dog Corresponding in part of their respective solubilities, differing effects on tissue from local application of sulfanilamide and sulfathiazole are now recognized⁸ A clinical impression exists that similar differences occur with the use of the two drugs in the human peritoneum¹⁵ Part of the present study was devised to determine the relationship of sulfanilamide and sulfathiazole to the production of adhesions in the intact peritoneum of the dog

During the past three years we have reported extensive series of experiments in the dog, demonstrating that heparin locally applied is an effective agent in the prevention of the reformation of divided intraperitoneal adhesions^{5, 6, 7} Since heparin might be indicated in the contaminated peritoneum for the prevention of adhesions, a second part of the present study was directed towards the estimation of the reformation rate of adhesions following the combined use of heparin and sulfanilamide

METHODS

In all experiments mature mongrel dogs were used Intraperitoneal and intravenous nembutal (Abbott) was the anesthetic agent The skin antiseptic was Novak's solution⁹ Aseptic technic was followed throughout Adhesions were created by scarification⁷ and were divided by sharp dissection six weeks later Hemostasis within the peritoneal cavity was effected by either silk ligature or electrocoagulation The abdominal wall was closed in layers with silk

The experiments consisted of three groups (1) The effects of sulfa-

* Read by title before the American Surgical Association, Cincinnati, Ohio, May 13-14, 1943

Aided by a grant from the John and Mary R Markle Foundation

thiazole and of sulfanilamide in the normal abdomen (2) The effects of sulfathiazole and of sulfanilamide on the reformation of divided adhesions (3) The effect of heparin combined with sulfanilamide on the reformation of divided adhesions

The results were determined by a count of adhesions at celiotomy at least six weeks after the application of the various drugs

The following experiments were performed

I *Normal Abdomen*—A Control Dogs were subjected to celiotomy and the bowel and omentum were eviscerated onto warm moist towels. After the viscera were returned to the abdomen the wound was closed. B Scarification An attempt was made to create adhesions by extensive scarification of peritoneal surfaces. C Dry Sulfathiazole Upon opening the peritoneum, the bowel and omentum were delivered and laid on warm moist towels. Sterile dry sulfathiazole (Squibb) was evenly sprinkled over the bowel as it was being returned to the abdomen, the amount used being calculated on the basis of 0.5 grams per kilogram of body weight. D Dry Sulfanilamide Sterile dry sulfanilamide (Winthrop) was employed in the same manner and in the same dosage.

II *Division of Adhesions—Sulfathiazole and Sulfanilamide*—A Dry Sulfathiazole Adhesions were created by scarification of the peritoneum and some weeks later the abdomen was reopened. After separating the adhesions, sterile dry sulfathiazole or sterile dry sulfanilamide was sprinkled evenly over the involved portions of the small bowel as it was returned to the abdomen. The dosage was again 0.5 Gm per kilogram of body weight. B Concentrated Sulfanilamide Solution A saturated solution of sulfanilamide in normal saline was administered intraperitoneally by paracentesis after division of adhesions and for the first three postoperative days. One hundred and fifty cubic centimeters were given daily, either in a single dose, or divided into two doses at 12-hour intervals.

III *Division of Adhesions—Heparin and Sulfanilamide* A solution containing heparin* and sulfanilamide was given by paracentesis after the division of adhesions, and on three successive postoperative days. The total daily dose consisted of 150 cc of a solution containing 1.2 Gm of sulfanilamide (0.8 per cent) and 30 mg (3,000 anticoagulant units) of heparin. In some experiments this amount was given once daily, and in others it was divided into two doses at 12-hour intervals.

RESULTS

I *Normal Abdomen*—The average number of adhesions created by the simple introduction of dry sulfathiazole was 6.3. This compares unfavorably with an average adhesion formation of 5.0 resulting from scarification of the peritoneum in 51 dogs carried out with the object of creating adhesions. With dry sulfanilamide, however, the average number of ad-

* The heparin employed was Liquaemin, furnished by the courtesy of Roche Organon, Inc.

hesions formed was only 16 which compares with an average of 11 adhesions resulting from simple celiotomy. In the sulfathiazole experiments every animal presented at least one adhesion, whereas in the sulfanilamide experiments eight animals out of fifteen presented no adhesions (Chart 1)

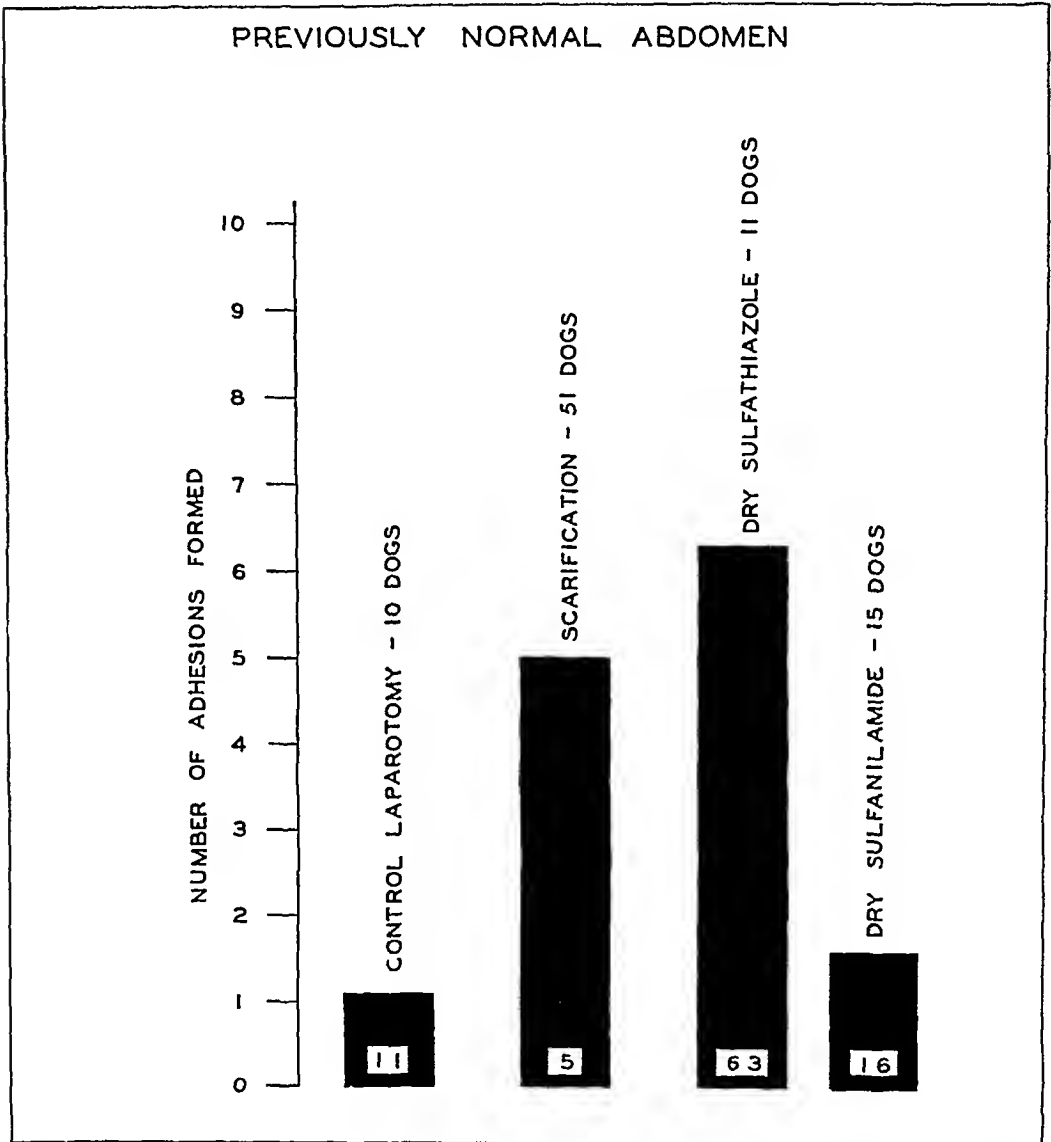


CHART 1—Effect in the dog of dry sulfathiazole and dry sulfanilamide in the creation of adhesions in the otherwise normal abdomen

II *Division of Adhesions—Sulfathiazole and Sulfanilamide*—In both groups of experiments with the dry preparation, the use of the drugs resulted in a greater number of adhesions than were divided. Following the use of sulfathiazole the average percentage of reformation was greater than 225 per cent, following the use of sulfanilamide it was greater than 175 per cent. The percentage of reformation cannot be given accurately because more adhesions were formed in nearly half the animals than could be counted.

Such animals were given a flat count of 20 adhesions, although they had more, usually many more, than that number.

With sulfanilamide solution, the results were somewhat more favorable, namely a reformation rate of only 100 per cent. There was no difference in the results between the animals given the drug once or twice daily. Both groups are, therefore, recorded together (Chart 2).

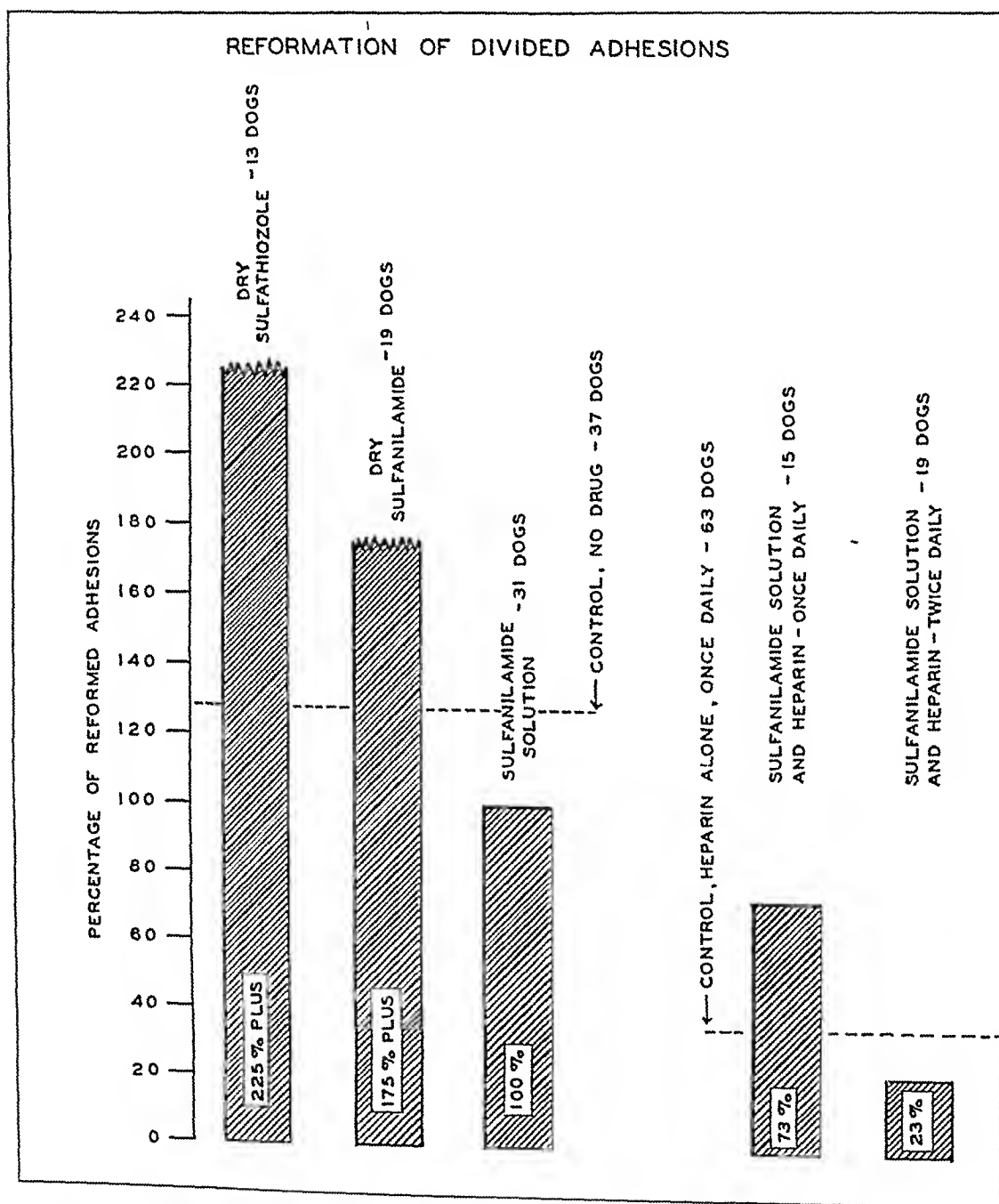


CHART 2—Effect in the dog of dry sulfathiazole, dry sulfanilamide and sulfanilamide solution, with and without heparin, on the reformation of divided peritoneal adhesions. The broken lines at the upper limits of columns one and two indicate that the actual numbers of adhesions were greater than the heights of the columns indicate. All animals in which the numbers of adhesions were greater than 20 were counted as 20.

III Division of Adhesions—Heparin with Sulfanilamide—In these experiments there was improvement over the results with sulfanilamide alone. A striking difference was observed in the number of adhesions which reformed.

depending on whether the solution was administered once or twice daily. When given once daily, the average rate of reformation was 73 per cent, and when given twice daily, it was 23 per cent.

DISCUSSION

The results of these experiments indicate a definite tendency on the part of dry sulfathiazole to create adhesions in the intact abdomen of the dog. Sulfanilamide is apparently less active. The effect of sulfathiazole is even greater than that of purposeful trauma to the peritoneum in the attempt to create adhesions, whereas the action of sulfanilamide is not significantly more harmful than the incidental trauma of simple celiotomy. The reaction to sulfathiazole may be a foreign body reaction related to the relative insolubility of the drug.

Following the division of adhesions, the deleterious effect of sulfathiazole appears to be markedly exaggerated. Curiously enough, dry sulfanilamide, although practically harmless in the intact abdomen, seemed in these experiments to be definitely active in reforming adhesions. The percentage of adhesions reformed is considerably greater than the average number reformed without the use of any drug (127 per cent), as reported in previous studies.⁷ However, when sulfanilamide is exhibited in solution, even though it is readministered as often as twice a day for three successive days, the drug seems to have no great effect in modifying the reformation of adhesions. When given in this form 100 per cent of adhesions reformed.

When heparin and sulfanilamide were combined and given once daily, the results were not as good as with heparin alone, *i.e.*, 73 per cent reformation as compared with the previously reported 37 per cent reformation.⁷ When, however, the same combination was given twice daily, the results improved tremendously, to an average of 23 per cent reformation. We have no figures for comparison of this last result with the use of heparin alone given twice daily. It is believed, however, that the favorable effect is due to the more continuous presence of heparin in the peritoneal cavity during the period of exudation.

In summary, these results suggest that sulfathiazole has a marked effect in tending to create adhesions in the peritoneum, and that sulfanilamide has a less harmful effect. The results of the experiments suggest, further, that from the point of view of adhesion formation sulfanilamide may be used more safely in solution than as the dry substance. What the effect of the drug in solution may be upon contamination of the peritoneum is a question not answered here. Before adopting clinically the use of the solution instead of the dry substance, experimental evidence should be available on its bacteriostatic effect in the peritoneum.

It is not believed that these experiments indicate the cessation of the current practice of using dry sulfanilamide in the peritoneum when necessary. The evidence presented, however, suggests sufficient danger of ad-

hension formation with sulfanilamide to warrant its use in cases in which its bacteriostatic effect is urgently needed. If these experiments on the dog are applicable to the human being, the use of sulfathiazole in the peritoneum would seem to be positively contraindicated.

It must be recognized that the present experiments are conditioned by only that degree of contamination of the peritoneum which is incidental to all clean celiotomies. The effects of the drugs in the infected or contaminated peritoneum have not been examined in this study. In view of the fact that peritoneal infection is one of the commonest causes of adhesion formation, it is easy to see why both experimenters and clinical observers have gained the impression that sulfanilamide has a tendency to decrease the number of adhesions. The diminution of adhesions following peritonitis through the use of sulfanilamide might readily be predicted from the activity of sulfanilamide in controlling infection rather than from any direct virtue in the drug as an adhesion preventative.

Summary 1 The application in the dog of dry sulfathiazole to the peritoneal surfaces in the intact abdomen and after the division of adhesions results in marked adhesion formation.

2 Dry sulfanilamide when applied to the intact peritoneal surfaces creates few adhesions. However, when applied following division of adhesions, a definite tendency towards adhesion reformation is observed. In solution, the tendency towards adhesion reformation is much less marked.

3 A solution of sulfanilamide and heparin has a slight protective effect against adhesion reformation when exhibited once daily after division of adhesions. When given twice daily, an excellent protective effect is observed.

CONCLUSIONS

1 In view of the evident tendency of sulfathiazole to create peritoneal adhesions in the dog, it should probably not be exhibited intraperitoneally in the human being.

2 Sulfanilamide in solution may offer less danger of peritoneal adhesions than the commonly used dry substance.

3 The reported experiments tend to confirm the effectiveness of heparin in preventing reformation of divided adhesions.

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CHANGES IN BRAIN VOLUME AND BLOOD CONTENT AFTER EXPERIMENTAL CONCUSSION¹

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IN RECENT SURVEYS of acute cranio-cerebral trauma McConnell,¹ and Guidjian, Webster, and Arnkoff² have reviewed the conditions which cause the brain to swell. The two basic factors concerned are intracerebral hemorrhage or congestion of the cerebral vascular tree and swelling of the cerebral tissue by extravasation of fluid into the cells or intercellular spaces. Increase in brain volume due to a single large clot or multiple petechial hemorrhages has been recorded frequently and does not require experimental confirmation. There is also the possibility of vascular congestion, which has not been thoroughly explored. While there is common agreement that localized edema occurs in an area of cerebral contusion, there is a wide divergence of opinion as to whether extravasation of fluid through the capillary walls occurs throughout the brain. Reichardt,³ who discussed the problem of brain swelling and edema in 1927, concluded that these reactions could not be produced experimentally because of the biologic differences between animal and human brains. To date, experimental trauma has failed to produce any clear-cut proof that capillary permeability is generally increased. The most impressive investigations in this field have been made by Pilcher,^{4, 5} who was unable to find any evidence in dogs of increased water content in the cerebral gray or white matter on dehydration to constant weight. In Pilcher's experiments the brain was traumatized by dropping a weight on the animal's head which was rigidly fixed in a head-holder. More recent work has shown these experiments to be open to two serious criticisms. The investigations of Denny-Brown and Russell⁶ have proved conclusively that cerebral concussion does not occur when the head remains stationary. Its production requires sudden acceleration or deceleration, such as occurs when the moving head encounters an unyielding object, or the stationary head is struck by a moving one. Therefore, in Pilcher's experiments, which were made under a general anesthetic, it is most unlikely that concussion could have developed. It is unfortunate that no record of posttraumatic changes in reflexes are given in his protocols. Furthermore, Alexander and Looney,⁷ in a critical survey of methods of quantitating changes in brain volume, have pointed out that the presence of cerebral edema cannot be detected with certainty by the method of dehydration. The development of improved experimental methods and the importance of a better understanding of the pathologic changes which follow intracranial injuries have led us to reopen this problem in the laboratory.

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METHODS

Accurate methods of determining changes in volume of the brain and the blood content of the cerebral vascular tree in cats have been reported in a previous article by White, Verlot, Selverstone, and Beecher⁸ The correlation of brain volume with the capacity of the cranial chamber, originally suggested by Reichardt, was found by Alexander and Looney to be the most accurate index of variation from the normal cerebral volume in postmortem subjects White and his coworkers adapted this procedure to cats and found it to give extremely consistent results After decapitation and exsanguination the brain of the normal cat is from 10 to 12 per cent smaller than the surrounding cranial cavity For convenience we shall hereafter refer to this ratio as the differential index of brain volume (D I B V) This space is occupied by the meninges and cerebrospinal fluid in the subarachnoid space cisterns, and ventricles

The content of blood in the cerebral tissues was determined by a method adapted by Selverstone,⁸ from Bing and Baker⁹ At the moment of decapitation the neck of the animal is compressed by a powerful crushing clamp to prevent the loss of blood, and then frozen solid in dry ice After splitting the skull and removing the frozen brain, the content of blood is determined by comparing the color reaction of hemoglobin (extracted from the macerated brain by distilled water and saponin) with benzidine against a standard prepared from a sample of the animal's own blood The blood volume amounts to about 0.4 cc in the brain of the normal animal, and is reduced to about half this amount after exsanguination

Cats which were to be submitted to experimental concussion were anesthetized with nembutal (pentobarbital sodium) administered intraperitoneally (30 mg per kilo) This dose, supplemented if necessary by additional small amounts, ensures continuous light anesthesia, with preservation of reflexes over the period of the acute experiment In their previous investigation White, Verlot, Selverstone, and Beecher found that with this dosage of barbiturate, under normal conditions, there was no alteration in cerebral volume or blood content When severe degrees of anoxia (arterial oxygen saturation reduced to 40 per cent) were introduced, the brain volume increased as much as 5 per cent, *viz.*, the normal differential index between brain volume and intracranial capacity was reduced from 11 to 6 per cent While anoxia caused no congestion of the cerebral vessels, a 10 per cent rise in the carbon dioxide content of the inspired air doubled the amount of blood in the cerebral vascular tree It was, therefore, important to prevent anoxia or hypercapnea This was done by inserting an intratracheal cannula In order to avoid any error, the oxygen saturation of the arterial blood and its carbon dioxide content were determined before the animals were killed

As shown by Denny-Brown and Russell, a relatively constant degree of cerebral concussion can be produced by striking the animal a blow over the occiput with a swinging pendulum The apparatus which we used was

designed by Professor Nathaniel H Frank, of the Physics Department, Massachusetts Institute of Technology (Fig 1) The striking speed of the pendulum is accelerated by heavy metal disks which are mounted eccentrically on an axle suspended on ball bearings To obtain a slightly greater speed at impact we added a spiral spring attached to one of the disks The striking speed of the pendulum, when released from various angles, was calculated by the number of vibrations of a tuning fork recorded on a 12-inch length of smoked paper We did not attempt to calculate the energy produced on impact of the pendulum at various striking speeds, because its relation to concussion has been considered by Denny-Brown and Russell

After the induction of anesthesia, the cat was placed on its side in position for the standard blow on the occiput Pulse, respiration, size of pupil (in millimeters), light and corneal reflexes, and the knee jerk were recorded, the animal being observed until these observations remained constant The pendulum was then released Travelling at a speed up to 465 feet per second (317 miles per hour), it produces an intense blow which is sufficient to spin the animal around and throw him several feet across the table After the trauma we repeated the above recordings of the heart and respiratory rates, size of pupils, and the reflexes at 15- to 30-second intervals until they returned to normal A cistern puncture was then performed, and recordings of spinal fluid pressure made at regular intervals In addition, rectal temperatures were taken and warmth applied as necessary, in order to prevent an excessive loss of body heat At the end of varying intervals the animals were killed by decapitation with a special shears previously described⁸ This permitted

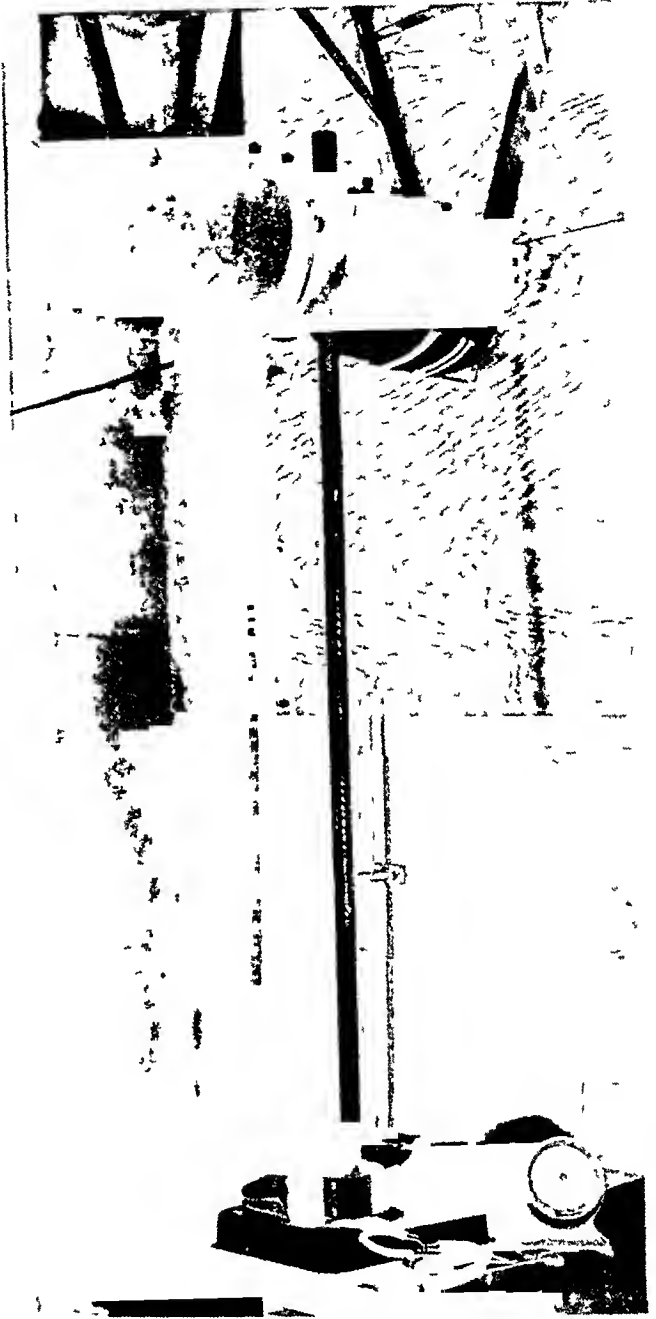


FIG 1—The pendulum used for producing experimental cerebral concussion The cat is shown in position for trauma to occiput

exsanguination of the head in the case of determinations of brain volume, or crushing of the neck and retention of blood in the head in cases where determinations of cerebral blood volume were to be carried out

CEREBRAL VOLUME CHANGES AFTER CONCUSSION

A total of 24 cats have been used in these experiments. Of these, one was not traumatized, and the results in three had to be discarded, because of the presence of "snuffles" in Cats Nos 153 and 154 and because the medulla was punctured in the course of cisternal puncture in Cat No 151. It was felt that valid deductions on the effects of trauma on cerebral volume could be drawn from the remaining 20 animals.

In the earlier studies of White, Verlot, Selverstone, and Beecher it was found that the volume of the brain in four unanesthetized cats after exsanguination was on the average 10.5 per cent less than that of the cranial cavity. As a result of further experience we feel that this differential index of brain volume should be increased slightly, as we have found variations between 9.9 and 12.1 per cent, with an average figure of 11 per cent. The administration of pentobarbital sodium intraperitoneally caused no change in the volume of the brain, provided the oxygen saturation of the blood remained at normal levels. It has also been shown that exsanguination reduces the intracerebral blood content to a very constant residual of 0.20 cc.

The degree of concussion in lightly anesthetized cats was determined by following the changes in respiration and heart rate, the size of the pupils, and the return of the corneal and light reflexes, as suggested by Denny-Brown and Russell. The severity of concussion was graded 1, 2, or 3+, depending on the physiologic disturbances after the blow. The characteristic response was a brief period of apnea and then a recovery of the normal rate and depth of respiration. The heart rate was at first usually reduced, up to a maximum of 72 per cent, but occasionally there was a slight acceleration. Irregularities in the heart beat were frequent. The corneal reflex was consistently lost, but recovered in a period of from a few seconds up to two minutes. Dilatation of the pupil and disappearance of the light reflex roughly paralleled the loss of the corneal response. In no case were the knee jerks abolished. With the exception of Cat No 140, where respiration failed to return, the animals appeared to have fully recovered within a period of two to four minutes. When Cats Nos 147 to 152 (inclusive) were allowed to come out of the anesthesia, they showed no evidence of any ill effects from the concussion.

We found that pendulum-striking speeds of less than 30 feet per second failed to produce consistent evidence of cerebral disturbance. On the other hand, speeds of 46.5 feet per second caused pronounced reflex changes, basilar hemorrhages,* or occipital fractures in three animals. Of these, Cats Nos

*This subdural and subarachnoid bleeding did not interfere with the measurement of brain volume, as the blood was thoroughly evacuated before the determinations were made. It may seem unfair to classify animals with basilar hemorrhages in the category of simple concussion. This is done because there was never any evidence of laceration or contusion of the brain and because the bleeding seemed to come from vessels in the upper cervical region.

TABLE I

SUMMARY OF DATA AFTER CEREBRAL CONCUSSION IN CATS

Cat No	Age*	Speed of Blow Feet/Sec	Period of Apnea		Change in Cardiac Rate %	Pupillary Dilatation Mm	Loss of Reflexes		Concussion	Survival Period	D I B V %	Cerebral Swelling %	Comment
			Min	Sec			Corneal	Light					
131	Adult	34	1	30	+11	2 to 6	2 min	2 min	++	5½ hr	7 6	3 4	No visible post-mortem change
132	Young	34		30	-32	5 to 7	1 min	1 min	++	3 hr	7 3	3 7	No visible post-mortem change
133	Young	34	None		-19	0	few sec	0	+	3 hr	8 2	2 8	No visible post-mortem change
134	Adult	43	1		-33	0	1 min		++	26 min	7 6	3 4	No visible post-mortem change
135	Young	43		40	-25	5 to 10	30 sec	45 sec	++	3 hr	7 4	3 6	Subgaleal clot Blood over cerebellum
136		43	1	30	-72	4 to 8	90 sec	90 sec	+++	5 hr	5 9	5 1	Occipital suture sprung Small subdural clot
137	Adult	43	Few sec		-25	0	Few sec	Few sec	+	3½ hr	11 8	0	Subgaleal clot Blood around brain stem
138	Young	43	1		-45	3 to 8		3 min	++	5 hr	8 5	2 5	Occipital fracture with blood around brain stem
139	Adult	46 5	1	10	-57	6 to 10	2 min		+++	30 min	9 4	1 6	Respiration not normal for 9 min Blood clot under pons
140	Adult	46 5	To death		-62	4 to 8	No recovery		+++	6 min	9 0	2 0	Blood from ear Clots along brain stem
141	Adult	43	None		-7	0	0	0	0	6 hr	10 7	0	Clot under scalp
142	Adult	46 5	30		-30	0†	1 min	4 min	++	4 hr	6 6	4 4	Bled from nose Occipital fracture
147	Young	43		7	-5	2 to 8	1 min	2 min	++	24 hr	5 4	5 6	No visible post-mortem change
148	Young	45		10	+20	3 to 8	15 sec	1 min	+	24 hr	7 2	3 8	Subgaleal and posterior fossa clots Occipital suture sprung
149		43		36	-29	1 to 5	40 sec	45 sec	++	30 hr	7 1	3 9	Subgaleal bleeding and film of blood around brain stem
150	Adult	45	1	30	+20	2 to 8	90 sec	4 min	++	30 hr	7 9	3 1	Subgaleal bleeding and film of blood around brain stem
151	Omitted from series because medulla was punctured												
152	Adult	43		15	-29	5 to 8	1 min	2 min	++	78 hr	11 6	0	No visible post-mortem change
153	Omitted from series because of snuffles												
154													
155	Young	Control animal given second dose of pentobarbital sodium at 23 hrs								24 hr	10 7	0	No visible post-mortem change
156	Adult	45		50	-45	4 to 10	100 sec	50 sec	++	3½ min	12 1	0	Small subgaleal and posterior fossa clots
157	Adult	45		45	-33	6 to 10	2 min	2 min	++	5½ min	11 7	0	Small subgaleal clot
158	Adult	45	1	15	-62	7 to 8	2 min	45 sec	++	16 min	8 0	3 0	Small subgaleal clot

Cats 143 to 146 (inclusive) were used for another type of experiment

The dilated pupils returned to normal size with recovery of the light reflex

With the exception of Cats 139 and 140 heart rate and respiration returned to normal in under 2 minutes

* Age of animals was estimated by examination of teeth No old or very young animals were used

† Pupillary enlargement was masked by the fact that the pupils were dilated before concussion

139 and 142 recovered within the usual four-minute period, but Cat No 140 died in six minutes of respiratory failure. Out of nine cats submitted to a striking speed of 43 feet per second (just under 30 miles per hour), one showed a slight separation of the occipital sutures, and five showed hemorrhages around the brain stem and cerebellum. On the whole, striking speeds of from 43 to 45 feet per second seemed to be the most satisfactory and to give fairly consistent moderate degrees of concussion. These speeds are somewhat higher than those recorded by Denny-Brown and Russell, who found that evidence of concussion followed a striking speed of 28 feet per second.

The protocols of the 20 satisfactory animals, with varying degrees of cerebral concussion, are shown in Table I. We have deduced the volume of cerebral swelling from the shrinkage of the free space between the brain and the cranial cavity. As the brain in the normal animal or the cat under light pentobarbital sodium anesthesia is from 10 to 12 per cent smaller than the surrounding cranium,[†] a reduction of this differential index of brain volume from 11 to 6 per cent represents an expansion of the brain mass of 5 per cent. This figure cannot be influenced by vascular congestion, because it has been shown that the blood content of the exsanguinated brain is reduced to a very constant level,⁸ and this was corroborated by microscopic examination of the benzidine-stained sections. A further theoretic cause of error could be distension of the ventricles by abnormal amounts of cerebrospinal fluid, as mentioned by Arnaud,¹⁰ and other continental writers. In the previous studies of White, Veilot, Selverstone, and Beecher, hydrocephalus was routinely sought for, but no evidence of it was ever detected. Furthermore, it was observed that in the course of removing the brain from the skull the ventricular cavities were very nearly emptied of their fluid content. To verify this observation we have weighed the traumatized brain after its removal from the skull and then cut it transversely to open the lateral and third ventricles. After drying these carefully with bits of absorbent cotton and reweighing, we have found that the weight of the retained ventricular fluid amounted to no more than 0.15 to 0.25 Gm.

A study of the data in Table I shows that, although exactly comparable degrees of concussion were not produced by a given speed of acceleration of the animal's head, the amount of swelling of the brain corresponded very definitely with the posttraumatic changes observed. Striking speeds of 34 feet per second in three cats (Nos 131, 132, and 133) produced a 2+ grade of concussion in two and a milder degree in the third. The greatest swelling occurred in Cat No 132, and amounted to 3.7 per cent. In this animal the period of apnea lasted 30 seconds, and normal respiration had recovered at 45 seconds. The heart rate was reduced 32 per cent and remained irreg-

[†] As it is impossible to determine the volume of the brain before trauma, the only available figure for comparison is the average differential index in the normal animal. This objection is obviated to some extent by the small degree of variation observed.

ular for one minute. There was only slight dilatation of the pupils, and the corneal and light reflexes recovered in 60 seconds.

Striking speeds of 43 feet per second in nine animals failed to produce any definite signs of concussion in Cat No 141, and only very mild concussion in Cat No 137. Neither of these animals had swollen brains. In the four other cats observed over periods of from 26 minutes to five hours, brain swelling was definite, and varied from an increase of 2.5 per cent in cerebral volume to 5.1 per cent. In this latter animal (Cat No 136) apnea lasted 90 seconds, and the heart rate was reduced 72 per cent. The corneal reflex was lost, the pupils remained dilated, and the light reflex disappeared for 90 seconds. This animal had a sprung occipitoparietal suture and a small clot under the brain stem. There was, however, no gross evidence of cerebral contusion. When the striking speed was stepped up to 46.5 feet per second in three animals, concussion ranged from 2 to 3+, but the increase in brain volume in the two cats which survived less than 30 minutes was slight. The reason for this is explained below. In the third animal, where there was a 2+ degree of concussion, the brain volume increased 4.4 per cent before decapitation four hours later. This animal was apneic for 30 seconds, and required 60 seconds to recover its normal respirations and corneal reflex. The heart rate was reduced 30 per cent, but returned to normal in four minutes. Postmortem examination showed a linear fracture running across the occiput, but there was no evidence of gross contusion of the brain.

A second point of interest is the time required for posttraumatic cerebral swelling to develop, reach its peak, and subside. When the brain volume was measured 3.5 to 5.5 minutes after moderately severe degrees of concussion in Cats Nos 156 and 157, it remained within normal limits. In Cat No 140, after a very severe concussion, which resulted in death from respiratory failure in six minutes, there was only 2 per cent increase in cerebral volume. In Cats Nos 158 and 134, which were killed 16 minutes and 26 minutes after traumatization, and had 2+ degrees of concussion, there was an increase in cerebral volume of 3 and 3.4 per cent, respectively. In the four cats that were sacrificed at 24 to 36 hours,* the greatest degree of swelling seen in any animal (5.6 per cent) occurred in Cat No 147, where concussion was moderate in degree (2+), and the animal killed 24 hours afterwards. This animal showed only a seven-second period of apnea, and a slight (5 per cent) decrease in heart rate, but the pupils dilated from 2 to 8 mm and the corneal reflex was lost for one minute. On recovery from the anesthetic, it showed no signs of discomfort and no evidence of any neurologic abnormality. Cat No 152 was allowed to survive for 78 hours, and then was found to have a normal-sized brain.

The relationship between time elapsing after trauma and cerebral swelling is shown in Figure 2. McConnell's¹ findings in human cases of closed head

* Whenever animals were permitted to recover from the anesthetic, they were re-anesthetized before decapitation. A control cat (No 155), submitted to a second dose of intraperitoneal pentobarbital sodium, was found still to have a normal-sized brain.

injury are of interest in this respect. He states that "generalized swelling or edema of the brain was found soon after the injury and during recovery. It was not related to the state of consciousness. In this series of cases cerebral edema did not appear to increase the effects of the basic lesion of concussion or to delay recovery from concussion." This statement applies

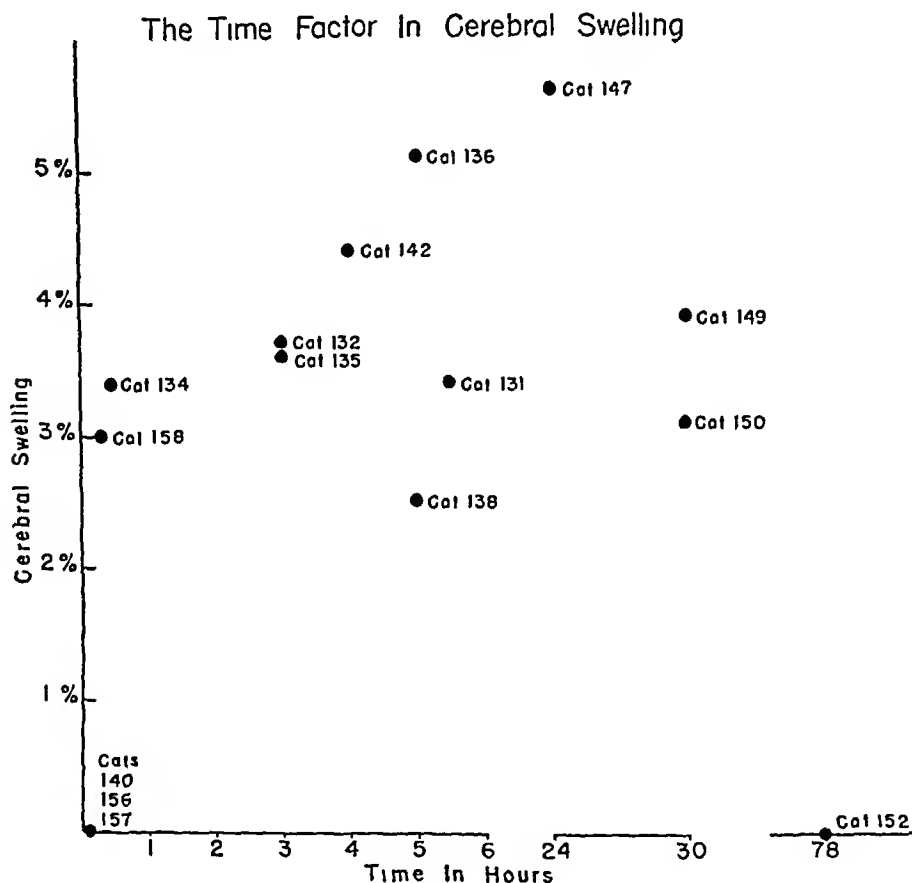


FIG. 2.—Relation between cerebral swelling and the time elapsed after concussion

equally well to our findings after experimental trauma. During the first few minutes after the cat's head was struck the reflexes were abolished and consciousness would undoubtedly have been lost in an unanesthetized animal, as Williams and Denny-Brown¹¹ have demonstrated with the electro-encephalogram that the brain waves disappear over this period. But swelling is not an instantaneous process and did not develop to a measurable extent until all evidence of concussion had passed. Furthermore, as soon as the animals had thoroughly recovered from the anesthetic, they showed no evidence of discomfort or neurologic disturbance, in spite of the fact that cerebral swelling was at its maximum.

BLOOD VOLUME CHANGES AFTER CONCUSSION

Analyses of intracerebral blood volumes have been made in ten cats. Half of these were normal control animals, and in the other five the analyses

CEREBRAL CONCUSSION

were made at periods of from 5 to 6.5 hours after concussion (the time at which brain swelling reaches its maximum). These determinations, recorded in Table II, showed no evidence of congestion of the cerebral blood vessels nor of extravasation of blood. The blood content of the brain varied from 4.33 to 0.44 cc, whereas in five normal animals it averaged 0.43 cc. These findings were corroborated by the microscopic examinations of sections of other traumatized brains stained with benzidine to bring out the erythrocytes (see section on "Pathologic Changes after Concussion").

TABLE II
CEREBRAL BLOOD CONTENT

Cat No	Velocity of Blow Feet per Second	Concussion	Blood Cc
<i>In traumatized brains *</i>			
159	45	++	0.37
160	45	+	0.23†
161	45	++	0.44
164	45	+	0.33
165	43	+	0.36
<i>In untraumatized controls</i>			
167			0.36
69			0.49
70			0.57
75			0.40
105			0.36

* The traumatized cats were killed after 5 to 6.5 hours

† Error probably due to inadequate grinding and extraction of blood from brain

Both Pilcher,^{4, 5} from his experiments on dogs, and Shapiro and Jackson,¹² from examination of brains of patients killed by cerebral trauma, concluded that posttraumatic swelling was largely due to an increase in the blood content of the brain. In Shapiro and Jackson's fatal cases cerebral contusion was severe enough to produce multiple petechial hemorrhages throughout the brain substance. But an increased blood content was not a factor in these cats with simple concussion, as chemical tests failed to show any increase in hemoglobin content and microscopic examination demonstrated neither petechial hemorrhages nor vascular engorgement.

CEREBROSPINAL FLUID PRESSURE CHANGES AFTER CONCUSSION

Determinations of the cisternal pressures were made in 14 animals, under light pentobarbital sodium anesthesia. In making these punctures the manometer was filled with isotonic salt solution to a point slightly below the normal fluid pressure. Eight cats served as controls and six others were submitted to trauma, all of which developed mild to moderate degrees of concussion (Table III). As it is a recognized fact that when two thecal punctures are performed with an interval of several hours the pressure in the second may be lowered because of leakage through the tract of the needle, we felt it best, as a rule, to perform only a single puncture and compare the pressure findings

TABLE III

HIGHEST RECORDED CISTERNAL PRESSURES IN CATS AFTER CONCUSSION

Cat No	Velocity of Blow Feet per Second	Concussion	Time after Trauma Hours	Increase in Brain Volume %	Cistern Pressure Mm of Normal Salt Solution
142	46.5	++	4	3.4	100
147	43	+	22½	5.6	75*
148	45	+	24	3.8	97
150	45	++	29	3.1	135
152	43	+	78	0	112
171	45	++	5		130

Cisternal pressures in eight untraumatized control cats under similar conditions 55 to 90 mm average 70 mm

* Needle leaked

in the traumatized animal with the average level in normal cats. In our eight control cats under light pentobarbital sodium anesthesia, cisternal pressures ranged from 55 to 90 mm of isotonic salt solution. When postconcussional cisternal pressure determinations were made at intervals ranging from 4 to 78 hours, pressures were found between 75 and 135 mm. In the final observation on Cat No. 171 the cistern was punctured before the occipital blow and the needle then reinserted and left in place during a five-hour period afterward. The spinal fluid pressure rose from an initial level of 80 to 130 mm (Fig. 3).

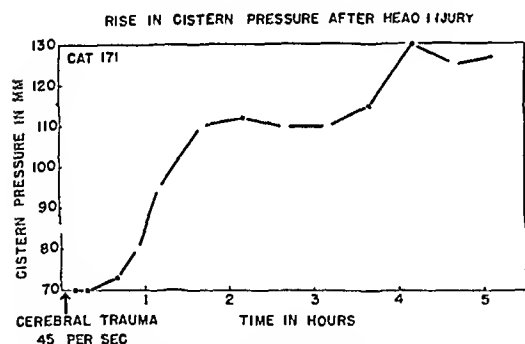


FIG. 3—Rise of cisternal pressure in Cat No. 171 in the five hours following experimental concussion of moderate severity.

In spite of the small series of animals in which these readings were made this evidence indicates that there is a slight to moderate rise in pressure after concussion and during the period in which the brain is swollen. The result in Cat No. 152 suggests that the elevation in pressure may outlast the period of actual swelling. In Pilcher's four dogs, where the fixed head was traumatized there was also a comparable rise in the cisternal pressure

readings. Our series is, unfortunately, small and it will be necessary to make further observations before exact conclusions can be drawn.

PATHOLOGIC CHANGES AFTER CONCUSSION

In the pathologic examination of these brains an attempt was made to demonstrate certain structural changes which could be correlated with the observed increase in cerebral tissue volume. Several investigators, among them Apfelbach,¹³ and Courville,¹⁴ have asserted that swelling of the oligodendroglia, enlargement of the perivascular and pericellular spaces, appearance of vacuoles in the white matter, hydropic changes in the cells of the ependyma and choroid plexus, are reliable indicators of traumatic cerebral edema. We,

therefore, prepared our material by technics best designed to show these alterations

Immediately after removal, one portion of the brain was placed in formalin-ammonium bromide solution and the remainder in ten per cent neutral isotonic formalin solution. The duration of fixation was 12 days, after which sections were stained by Penfield's combined method for oligodendroglia and microglia, Pickworth's benzidine technic for the vascular tree, cresyl violet and H and E for cellular detail, Weil's method for myelinated fibers, and the Gros silver technic for axis cylinders. On many of the cases Sudan II (Oil Red O) fat stain was done.

The microscopic sections were examined without knowledge of the severity of concussion or degree of brain swelling. In each section a careful search was made for the aforementioned criteria of cerebral edema.

It was quite apparent that there was no significant difference in the vascular pattern or the amount of blood in capillaries and veins between the most severely concussed brain and those which were not traumatized. Swelling of the oligodendroglia was found only in Cat No. 132. This was surprising, in view of the constancy with which it has been observed in local brain edema and other states. Enlargement of the perivascular and pericellular spaces was noted in Cats Nos. 132, 136, and 147. Of these three brains, the amount of swelling in No. 136 was very slight. Hydropic changes in the ependyma was most conspicuous in Nos. 132 and 141, in the former concussion was rated as 2+, and the latter received no concussion. Vacuoles were present in white matter of Nos. 132 and 133, and were slight in No. 147. One of these (No. 133) had only a slight concussion. The sections prepared by the Gros silver technic for axis cylinders were examined particularly for swelling, tortuosity, and fragmentation of nerve fibers. In none of the experimental animals were these changes observed. From these data we are forced to the conclusion that these histologic criteria are unreliable and unsatisfactory for the demonstration of the degree of brain edema produced in this experiment.

To test the hypothesis of Mahoney,¹⁵ that concussion is due to cerebral fat embolism, we made fat stains on several of the most severely traumatized animals. In none was there evidence of fat embolism.

DISCUSSION

Concussion, as recently defined by Gurdjian, Webster and Arnkoff, is "an unconscious state after head injury unassociated with macroscopic or microscopic lesions of the brain." If one may assume that the period during which the reflexes in these lightly anesthetized animals were abolished corresponds roughly with the period of unconsciousness, the disturbance produced was not severe. In the five animals permitted to recover from the anesthetic there were no signs of residual neurologic disturbance. Attempts to produce more severe grades of injury with definite contusion of the brain met with failure. Pendulum-striking speeds of 46.5 feet per second were the highest which the cats could survive. Such a blow was sufficient to produce linear

fractures in the occipital bone or bleeding from the ear, as well as hemorrhages around the medulla and cerebellum. Although this degree of trauma led to rapid death from respiratory failure in Cat No. 140, none of the three animals developed petechial hemorrhages in the gray or white matter, nor any other evidence of contusion. It is obvious that the small brain of the cat (average weight 26 Gm.) does not develop sufficient momentum to cause local bruising at the point of impact or by *contrecoup*. To accomplish this would require such a severe blow that the vital centers in the brain stem would fail to recover. The difference in vulnerability to trauma between the cat and the human brain is great. As shown above and by the experiments of Denny-Brown and Russell, it required a striking speed of approximately 20 miles per hour (30 feet per second) to produce concussion, and even rates of 30 miles per hour (44 feet per second) failed to produce prolonged disturbances in cerebral function. In man, on the other hand, falling from a hospital bed and striking the head on a hard floor has been a cause of concussion. At best, under these circumstances the head would undergo a free fall of three feet, and a striking speed of only 13.9 feet per second (9.5 miles per hour) could be attained. This greater vulnerability to trauma of the human brain is undoubtedly due to the larger brain mass and the contusing force derived from its greater inertia on sudden acceleration or its increased momentum on deceleration, not to any greater sensitivity on the part of the human nerve cells. As pointed out above, the histologic examination of the brains in these cats has shown no evidence of contusion. In man, contusion, and the obvious edema that may go with it, are limited to local areas where the bruising force has been exceptionally severe. It takes time to develop and cannot occur throughout the brain, because with such a severe injury death would be instantaneous.

After concussion it is evident that swelling of the brain follows much the same course as is seen in mild bruises in other parts of the body. It begins to appear within a quarter of an hour, reaches its maximum in from 5 to 24 hours, and subsides within three days. The quantitative method we have used in these and other experiments to measure cerebral swelling has given consistent results in over 100 animals, but one cannot differentiate between swelling of the cells themselves and extravasation of fluid into the intercellular spaces. For this reason we have refrained from specifying edema and have made use of the more inclusive term "cerebral swelling," but it must be emphasized that the permeability of the capillaries is not increased to the point where erythrocytes escape.

The swelling we have demonstrated after concussion does not seem at first glance to be very extensive, as it amounts to an increase in brain mass of less than 5.5 per cent. However, when one stops to consider the potential space available for expansion within the skull, it is evident that the intracranial cisterns and the cerebral ventricles must be definitely compressed. To understand this one must remember that the space within the cranium

contains not only brain tissue, but in addition the blood content of the cerebral vascular bed, the arachnoid and dural membranes, with the blood in the dural sinuses, and the cerebrospinal fluid which fills the remainder of the space. The quantitative relationships of these substances, in normal brains and also after concussion, are given in Figure 4. This shows that after a simple concussion the brain may swell to a point where it nearly fills the cranial cavity. The reason for the elevation observed in the cisternal pressures is, therefore, obvious.

Theories to account for the rise in intracranial pressure after head injury, expressed in previous articles (Pilcher^{4,5}, Arnaud¹⁰, Shapiro and Jackson¹²), have generally emphasized the importance of minute hemorrhages, congestion of the blood vessels, and the increase in intraventricular fluid, and have

minimized the possible escape of plasma through the capillary walls. That an increase in intra- and extravascular blood plays an important rôle in cerebral contusion goes without saying, but it certainly is not a factor in concussion. Careful weighing of the residual fluid content in the ventricles after these brains were removed from the skull has shown that internal hydrocephalus is equally unimportant. We have, therefore, reached the conclusion that even in uncomplicated concussion there is a widespread extravasation of the noncellular elements of the blood through the capillary walls, although the process is so diffuse that actual edema or cellular swelling cannot always be visualized microscopically.

In the earlier paper by White, Verlot, Selverstone, and Beecher,⁸ it was shown that anoxia, by itself, is capable of causing a 5 per cent increase in brain volume. Still further swelling may occur with a rise in the carbon dioxide content of the arterial blood. Hypercapnea is capable of producing such a congestion of the cerebral vascular tree that the blood content of the brain may be doubled. When these two factors work together, as they do during failing respiration and with an obstructed air-way, the cerebral volume may increase to the point where the entire available intracranial space is filled and the brain severely compressed. Whether cerebral swelling due to trauma is further augmented to a serious degree by complicating

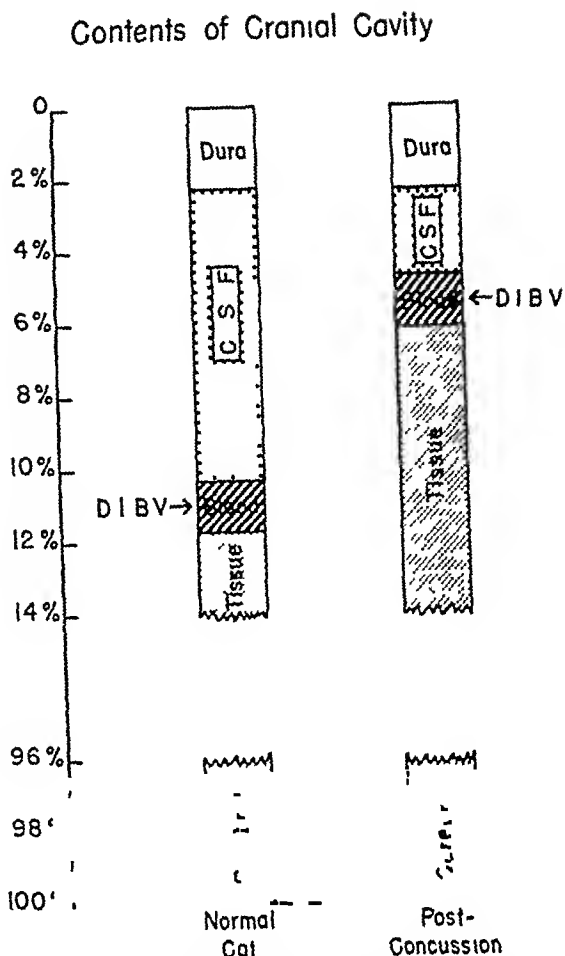


FIG. 4—The relative space within the cranium occupied by the brain, its blood contents, the dura, and the cerebrospinal fluid. Before and after concussion.

factors, such as a failure of the respiratory center, obstruction to the air-way, and respiratory depressant drugs, is to be the next subject for investigation

CONCLUSIONS

1 When cerebral concussion is produced in cats, for even brief periods, there is an increase in the volume of the brain up to a maximum of 55 per cent. The degree of swelling has been found to vary directly with the severity of the concussion. It makes its appearance in about 15 minutes, reaches its greatest extent between 5 and 24 hours, and subsides after three days.

2 Swelling of the brain is not related chronologically to the neurologic changes that accompany concussion. In these experiments it failed to develop until the respiratory, cardiac, pupillary, and corneal reflexes had returned to normal, and it reached its greatest extent after the animals had recovered from their anesthetic and no longer showed any evidence of residual cerebral disturbance.

3 After concussion the increase in brain volume is due to extravasation of fluid through the capillary walls, and not to the escape of red cells, to vascular congestion, or to distension of the ventricles with increased amounts of fluid.

4 The increase in cerebral volume reported has not been sufficient to produce the histologic changes which have been commonly regarded as characteristic of cerebral injury. There has also been no microscopic evidence of vascular engorgement or escape of red blood cells.

5 The degree of cerebral swelling is, however, sufficient to reduce the space occupied by the ventricular and subarachnoid fluid from its normal volume of 8 per cent of the intracranial cavity to 2 per cent. Coincident with this the pressure in the cisterna magna undergoes a slight but definite rise in pressure.

6 When there is, in addition, an area of contused brain, or when anoxia and a rise in the blood carbon dioxide level result from an obstructed air-way, failure of the respiratory center, or respiratory depressant drugs, further swelling and congestion of the brain may lead to serious compression of the vital centers.

We wish to take this opportunity to extend our thanks to Miss Anna Murphy and Miss Eleanor Fogerty, of the Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, for carrying out the blood-gas analyses.

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DISCUSSION—DR FRANCIS GRANT (Philadelphia, Pa) This paper of Dr White's represents a carefully controlled series of experiments Of particular value are the results he has obtained in the production of more severe types of concussion In experiments of this type in the past, control of the amount of applied injury has been difficult The usual result in our experience has been that either little or no apparent damage has resulted from the blow or that the animal has promptly died

To produce a state of prolonged unconsciousness in the animal that is at all comparable to the situation seen in man after severe cranial injury is very difficult, and only with the development of our ability to produce such experimental animals can we begin to study the fundamental causes of death following cranial trauma, why, for example, pulmonary congestion, hyperthermia and loss of peripheral vascular arteriolar control are so uniformly found in the terminal stages following cranial injury

That a sudden, sharp movement of the head through space will cause unconsciousness is common knowledge Many prize fights have confirmed this observation But an abrupt deceleration in the movement of the head is much more serious Then, a patient is thrown from an automobile or falls from a height, the movement of the head is suddenly and forcefully checked Injury now occurs in two areas At the point of immediate impact, and at the opposite pole, by contrecoup The brain is shaken inside the cranial vault like dice in a dice box Not only are there the coup and contrecoup injuries to the surface of the brain but a case of contusion stretches into the midbrain between these points of injury

Neither time nor inclination exists for the consideration of an exact definition of concussion Many gradations of unconsciousness plus recovery come under this defini-

tion We are all familiar with the football player who is knocked out momentarily, comes to his feet almost at once, plays magnificently in the last quarter, and on reaching the dressing room suddenly asks who won the game. He has no conscious recollection of anything that happened. He may and probably has had a concussion. He was apparently unconscious for a period but, then, except for his highest centers of memory and integration, he functioned apparently normally.

This is a situation which obviously cannot be reproduced in animals. But by this method of injury plus carefully coordinated studies of neurologic evidences of the degree of consciousness as shown by response to pain, abolition or retention of reflexes, plus microscopic indication of brain damage to definite areas, we may be able to determine, roughly at least, what degree of injury to what areas of the brain are necessary to produce the unconsciousness plus recovery we have termed concussion.

It is interesting in regard to these cases of Doctor White's that although the unconsciousness was immediate and the recovery was relatively immediate, the maximum swelling did not appear for some little time later on. So, obviously, the mild edema of the brain which he reported has had nothing to do with the momentary unconsciousness produced by the blow.

If I have any criticism of this paper it is that microscopic studies were focused on the presence or absence of evidence of edema and were not carried through the mid-brain as well as the cerebrum at the point of application of the violence.

That the application of violence to the head was followed by edema is not surprising, even in the absence of evidence of contusion of the adjacent cortex. The brain responds to injury by a certain degree of swelling commensurate with the degree of injury, exactly as does any other part of the body. In man, concussion is commonly followed by a headache, suggestive of mild brain swelling which, just as in Doctor White's animals, begins promptly, may be maximal in 24 hours, and then disappear. It is to be hoped that those who believe in lumbar puncture or dehydration will note rather the rapid disappearance of this edema than its occurrence, and permit the pressure to subside spontaneously instead of trying to hasten its fall by unnecessary removal of fluid.

Doctor White is to be congratulated on this work. He has developed and improved the methods described by Zucherman and Denny-Brown, and confirmed their findings. It is through basic work of this type that our knowledge of the underlying physiologic processes consequent upon cranial trauma will be increased and possible advances in our treatment of these conditions made.

WAR WOUNDS OF THE CENTRAL NERVOUS SYSTEM ¹

CAPTAIN W. M. CRAIG, ¹M. C., U. S. N. R.

THE RECOGNITION AND TREATMENT OF SHOCK, the use of the sulfonamides, the improved transportation of the wounded by air, land, and sea, and a more comprehensive conception of the physiologic effect of trauma have almost revolutionized the treatment of wounds of the central nervous system.

In previous wars the mortality in wounds of the brain was greatly increased by shock and infection. Transfusions of blood, plasma and albumin administered in sufficient quantities to combat shock have made possible the transportation of patients over long distances. The emergency treatment of open head wounds, consisting of shaving the scalp, arrest of hemorrhage and local application and oral administration of sulfonamides have allowed for an interval before reparative surgery is imperative of from 36 to 48 hours. These two factors have not only lowered the mortality and reduced the incident of infection but have changed the plan for the care of these cases. Hospitals far from the scene of battle can be utilized for reparative surgery and the patients transported to them. Postoperative care and rehabilitation can thus be carried out simultaneously.

Wounds of the spinal cord still produce marked disability, depending upon the severity of the lesion, but the factor of infection has been moderated. Spinal shock caused by wounds of the contiguous structures have been noted and under proper treatment have shown a tendency to recovery in a large percentage of cases.

Wounds of the peripheral nerves are, and will be, one of the major problems of the war. Injuries of the extremities comprise the majority of disabling wounds, and, naturally there is a high percentage of peripheral nerves involved. While at the present time an end-to-end anastomosis is the operation of choice, using nonabsorbable sutures, fibrin glue and nerve grafts are being investigated as to their efficacy.

Peripheral vasoneuropathy, or the so-called immersion foot, has been recognized as a disabling affection of the extremities occurring to men who have been adrift at sea. Degeneration of the peripheral nerves has been demonstrated in amputated feet and legs associated with pathologic changes in the veins and arteries. Adequate treatment has been followed by a minimum of permanent disability.

In the present war the ideal arrangement would be to establish neurosurgical centers at strategic points for the care of wounds of the central nervous system. However, because of the fact that our ships and hospitals

* The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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are so widely dispersed, this is impossible. While the Bureau of Medicine and Surgery have attempted to distribute the neurologic surgeons among the hospital ships and hospitals, it is important that physicians aboard ships, with the Marines, and at first aid stations, be made aware of some of the fundamentals of diagnosis and treatment.

A very definite program of instruction has been carried out at naval hospitals and particularly at the National Naval Medical Center where series of lectures are given covering the subjects which a medical officer should know.

In attempting to teach some of the fundamentals involved in the effects of trauma, we conceived the construction of an animated diagrammatic motion picture which would depict the result of applied force. We were fortunate in having in our studio one of Walt Disney's assistants who had enlisted in the Navy. When outlining this motion picture the exact transmission of force to the head, causing the different types of injury to the brain, had to be demonstrated accurately. Simultaneously with the drawings which were made, experiments were carried out upon monkeys in which the calvarium was removed and a lucite convex plate was applied over the brain. Motion pictures of the brain could be taken through the transparent cap showing the exact movements of the brain subsequent to the application of force to the skull. In this manner the drawings were made, and an animated, diagrammatic motion picture was made in the studio at the Naval Medical Center.

The motion picture illustrates the different effects of head trauma ranging from concussion to laceration of the brain. Depressed fractures which become infected through neglect or improper care have been illustrated with the subsequent invasion of the meninges, the development of meningitis and brain abscesses.

Open and closed head injuries, with scalp wounds and penetrating wounds, are shown to emphasize the pathologic lesion.

As the proper treatment of head injuries, especially in the patients who are unconscious, requires free air passages, the effect of transporting the patient in the prone or the supine position is shown diagrammatically, with regard to the prevention of anoxia and its deleterious effect upon the cerebral cells.

The film illustrating head injuries is but the first of a series to show the effect of trauma upon the spine and to the peripheral nerves. It is being shown as an educational feature in the instruction of medical officers who are being sent out to care for the wounded aboard ship, in the mobile hospitals, and with the Marines.

DISCUSSION—DR A W ADSON (Rochester, Minn.) I feel rather inadequate to discuss this paper, because our experience has had to do with patients in civil practice. I am very much impressed with the speaker's animated films and can see how valuable they are in the teaching of surgery.

I think perhaps I can appreciate the situation that confronts Doctor Craig and others who are called upon to teach special procedures to men with general surgical training. It is obvious that some of the teaching has to be rather fundamental, and certainly this method of teaching is a very effective one. Our experience with the

use of the silent movie has been most effective in teaching diagnostic methods and surgical procedures in neurology and neurosurgery

I should like to emphasize one point, and that is the value of oxygen in the treatment of patients with craniocerebral injuries. We have found it to be of inestimable value in relieving the state of coma or unconsciousness.

Nothing has been said about chemotherapy. I am convinced that chemotherapy is a most valuable adjunct in the treatment of war wounds. The administration of the sulfa drugs in the presence of compound fractures of the skull lowers the incidence of meningitis and other septic conditions.

I congratulate Doctor Craig on the development of these animated films. I am sure that they will be worth while, not only in the development of neurosurgery but in the development of other phases of surgery as well.

DR ALLEN O WHIPPLE (New York City) I do not pretend to discuss the neurologic phases of the subject, but I would like to say something about the possibilities of using the animated cartoon for certain types of teaching, as compared to the rôle which the so-called moving picture has had in the teaching of operative procedure.

I do not believe that we can teach surgery by the moving picture, at least the technic of surgery. That is too complicated a subject to teach by the moving picture. It always seemed to me it was like trying to teach a man to play the cello by a sound movie.

The animated cartoon, however, is an entirely different technic and offers certain possibilities which I think have not as yet been used. I speak particularly in regard to the demonstration of the embryology of the various systems.

We have with us, as one of our residents at the present time, a man who explored this field, to a certain extent, while he was a student at the Northwestern University Medical School, and he demonstrated, certainly in showing the development of the primitive brain, that it was possible to bring out certain features that are in chronologic order which cannot be demonstrated in any other way.

I am particularly interested in developing an animated cartoon of the development and rotation of the gastro-intestinal tract. I have to teach that about three times a year to the third-year students in Applied Anatomy, and I turn myself inside out and stand on my head three times a year trying to demonstrate the process to the students and I never get it across, but I know, in an animated cartoon, it can be done.

MR JEFFREY JEFFERSON (London, England) It is a great pleasure, naturally, to be here and to have the opportunity of hearing these discussions, to get a first-hand experience of the problems which suggest themselves to you as being most worthy of the focusing of attention, and to hear of the way in which you are attacking them, specifically in reference to this last paper of my old friend, Captain Craig.

Really, what Doctor Adson and Doctor Whipple said about the method practically covers the ground. I sat there, quite re-instructed again on some of the simplicities of surgery which always gave one pleasure to see at any time.

If I might, I would like to discuss a part of the paper which Doctor Craig did not give, that is, about the treatment of penetrating wounds.

Some of us, like myself, have had experience both in the last war and again in this, and we have been led to certain conclusions about them. I emphasize, I should agree with what Captain Craig said, of course, about the rapidity of the treatment, in which we all believe. But we are all astonished to discover that a number of patients treated with sulfonamide particularly intravenously, survived untreated despite delays in further treatment due to circumstances of war. Of course, an aspect of all planning which is most difficult to get right, is the difficulties of any particular operation, not just any particular war not just any particular exercise in one country rather than another but the difficulties of a particular operation. While we all subscribe most heartily to the notion of early treatment, we add that the treatment should be given by competent hands and that a certain amount of delay is wise if by doing so the patient gets better treatment than he does by immediate operation by less skillful surgeons.

So it has come about that a number of patients have been successfully treated who had no operation at all for a matter of days. One has to resist the temptation to which some have succumbed of concluding that perhaps we are quite wrong in thinking that early treatment is not necessary.

We have to avoid that. We have to watch and stick to our principles. Although even large numbers of patients should survive in this way there are probably a number of men who died by the wayside, of whom no record exists.

Then I come to the other point, and that is how one should best treat the penetrating wound. One thing has been apparent from all experience, and that is that suction is the most important of any surgical procedure that we have. That, as many remember, was introduced by Harvey Cushing in the last war, using a small rubber catheter. Even in many of our operations overseas, we have been able to supply them with power suction. The neurosurgeon, from his experience with the sucking out of portions of the brain and the section removal of the tumors, has been encouraged to suck out areas of damaged brain, a procedure which the general surgeon would have thought went beyond the boundaries of reason or perhaps of practicability. With the properly set apparatus it is possible to produce these large cavities, which permit filling with sulfanilamide powder. This is of great benefit to the patient in avoiding the draining sinuses or the edema, and allows for the subsequent rather low incidence of fungus.

Moreover, by doing so it is possible to remove all or most of the fragments and usually to get rid of the damaged tissue.

The last point is that most fatal infections are not cortical meningitis spreading from the edges of the wound but an infection which has spread from the wounded area as encephalitis. To avoid the setting up of encephalitis in damaged tissue, with the blood clot around about, one should completely excise this whole area by suction and leave that part of the wound as a kind of cavity always closing the wound.

We have had some discussion as to whether or not scalp wounds, head wounds, and penetrative wounds should be left open or whether they should be closed, and although the general principle of leaving a limb wound, a flesh wound, open has been completely accepted by everybody, it has been no less completely accepted that head wounds ought to be closed. Some have closed them one, two, or three days after wounding, after the very thorough kind of suction and clean-out that I have mentioned, and have obtained something that is not perhaps quite primary union but very closely approximating it.

In this brief time I can not do full justice to this subject, but I thought that those were two points that occurred to me as being worth while of emphasis—they are, once more. The fact that those infections occur through an encephalitis that involves the ventricles and then spreads through all the ventricular passages, everywhere, rather than by local spread, and the necessity for the complete clean-up of the wound by suction, with the addendum that it is our duty to see that the surgeons who have to deal with these cases have the right instruments with which to carry out the operation.

CAPTAIN W M CRAIG, MC, USNR (closing) War wounds of the central nervous system have responded so satisfactorily to the modern method of treatment that it has become important to stress certain facts in the teaching of medical officers of the U S Navy.

At the Naval Medical School, where a course of instruction is given, we have been working on a plan of using animated diagrammatic motion pictures in emphasizing the fundamental factors involved in these wounds. Having Walt Disney's assistant in the enlisted personnel of the Medical Corps, and working in our motion picture studio, we have outlined a program for the making of motion pictures to be adapted to sound. This afternoon I am presenting the section dealing with head injuries.

These pictures are being presented as an educational feature in the instruction of medical officers who are being sent out to care for the wounded aboard ship, in the mobile hospitals, and with the Marines.

I greatly appreciate the discussion which has been made with regard to this presentation, particularly by Mr. Jefferson. I am sure you have all set up an experiment in the laboratory, and when you try the experiment you find it is not complete. Mr. Jefferson referred to penetrating wounds of the head. We spent months of our time on that portion of the film, which still remains on the reel, because, evidently, the film separated just as we reached the penetrating wounds, which I had hoped to demonstrate. He very graciously emphasized the points of importance.

RECENT ADVANCES IN THE TREATMENT OF RUPTURED (LUMBAR) INTERVERTEBRAL DISKS¹

WALTER E. DANDY, M.D.

BALTIMORE, MD

RUPTURED LUMBAR INTERVERTEBRAL DISKS, discovered fifteen years ago, are now among the most common lesions coming to surgery. Their diagnosis and localization are simple, almost absolutely certain, and a cure is practically assured, and almost without risk. The story of the early development of this field is now well known but in the past three or four years both the diagnosis and treatment have been revolutionized. Only these recent all important discoveries will be considered here.

The diagnosis can now be made solely upon the history of low back pain plus sciatica down the back of the leg and occurring in attacks, nearly always the backache and the pain in the leg are intensified by coughing and sneezing during the acute stage of pain. In 95 out of 100 cases with such symptoms a ruptured disk will be the cause. Three other conditions may cause the other five per cent: (1) Spondylolisthesis (2%), (2) congenitally defective fifth lumbar vertebra (2%), and (3) tumors of the cauda equina (1%). A roentgenogram of the lumbar spine will diagnose or eliminate spondylolisthesis and a congenitally defective vertebra. Tumors of the cauda equina (1% of the total), therefore, give the only problem in diagnosis. The symptoms may not differ from those of a disk but the backache may be higher, and there is frequently loss or diminution of patellar reflex. Should a tumor be present a lumbar puncture will usually show xanthochromic fluid. Only the suspicion of a tumor justifies a lumbar puncture.

Only two examinations are important: (1) Roentgenologic—In addition to excluding or diagnosing the above lesions, positive evidence of a disk is frequently indicated in the lateral view by narrowing of an intervertebral space. (2) The Achilles reflex. This is normal in over half the cases, but when reduced or absent the disk is usually at the fifth lumbar. It is therefore, important, only for localization of the disk.

TYPES OF DISK

There are two types of disks: (1) Protruding, and (2) concealed (very slightly protruding or not protruding). The latter are twice as frequent as the former and it is their disclosure that has cleared the whole subject of disks. All of these will be missed if spinal injections of lipiodol, air, etc. are used for diagnosis. Their symptoms are precisely like those of the protruding disks. They can be found at operation just as unequivocally as the larger disks. Always the nerve root is adherent and the thinned ligament

¹ Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

overlying the disk gives a sense of fluctuation to the forceps. When the ligament is punctured the forceps dip into a big cavity of the necrotic disk.

All affected disks have two components (1) The necrotic interior, and (2) the part that protrudes or attaches itself to the nerve. The former causes the backache, the latter the sciatica.

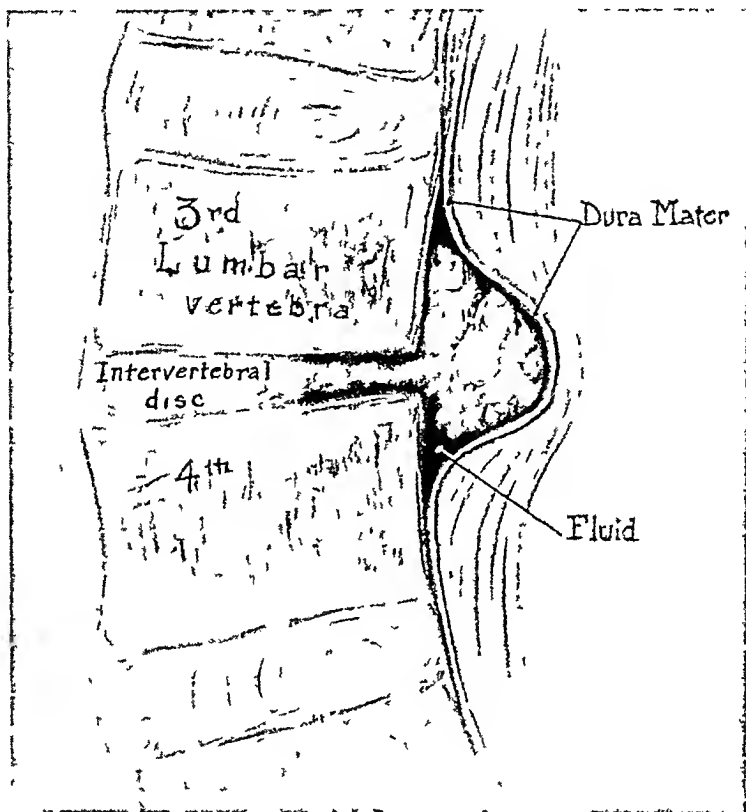


FIG. 1.—Drawing showing how the disk protrudes. The removal of the interior of the disk is all important unless thoroughly removed the percentage of recurrences will be very high.

SPINAL INJECTIONS OF LIPIODOL, AIR, ETC., CONTRAINDICATED

Until recently ruptured disks have been diagnosed and localized by spinal injections of lipiodol, thorotrast, air, *etc.* All are strongly contraindicated because they fail to disclose the small (concealed) disks which are two-thirds of the total. All disks can be diagnosed and localized without these contrast media, hence they are superfluous, moreover, if dependence is placed upon them the two-thirds that do not show by the injections are denied the cure that surgery affords. Spinal injections are painful and unless the liquid contrast media are removed they are permanent deposits having free access to all the fluid-containing spaces of the brain. Even spinal punctures contribute nothing and should be avoided.

LOCALIZATION OF DISKS

Ninety-eight per cent of all lumbar disks are at the fourth and fifth. This was first shown independently by Love at Mayo's, and Spurling, of

INTERVERTEBRAL DISKS

Louisville, and subsequent reports, including our own, have not changed this remarkable localization. This fact alone makes unnecessary any need for contrast media in the spine. It is almost as easy to explore both disks if it were necessary. But there are now methods of determining which of the disks is involved in over 90 per cent of the cases. If there is a diminution or absence of an Achilles reflex, the disk will be at the fifth in most instances. The roentgenogram shows a narrow interspace in many instances. When these tests are still negative, the affected disk can be localized at operation in

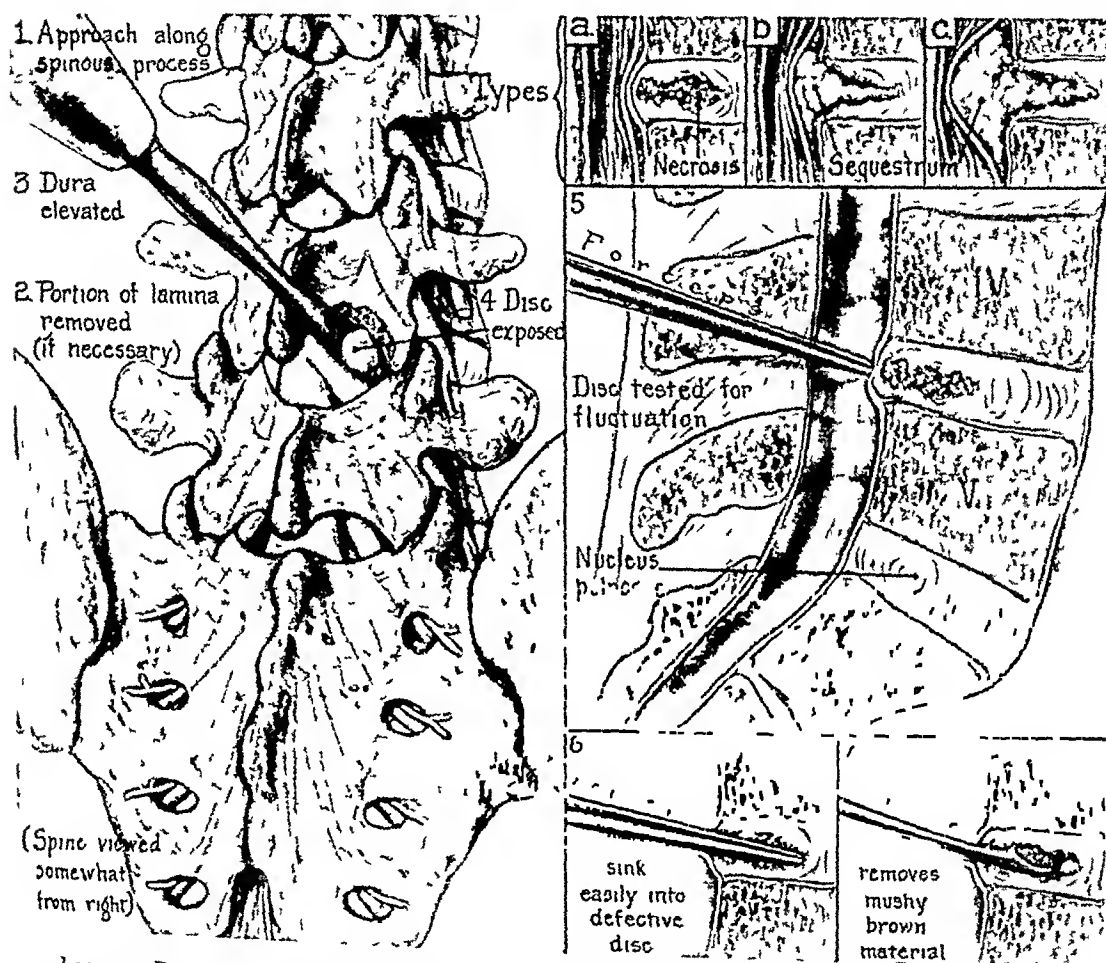


FIG. 2.—Drawing of a nonprotruding (concealed) disk. With experience, these are just as easy of recognition as the larger, protruding ones. The overlying ligament is thickened and white, and it fluctuates when the forceps press upon it. Moreover, it is usually quite adherent to the dura and nerve—*it* times quite densely so. When the forceps pass through the ligament a large cavity is entered, this is full of necrotic material—not infrequently large sequestra.

perhaps 85 per cent of the cases by horizontal pressure upon the spinous process. This determines the mobility of the joint, and a defective disk will nearly always cause an increased movement at the affected joint. The exceptions to this rule are in narrow intervertebral spaces shown roentgenologically, there may then be no mobility, or less than normal.

About 20 per cent of all patients with ruptured disks have two—one at the fourth and the other at the fifth. And since it is rarely possible to diagnose double disks before operation, the exposure of both is quite frequently done, especially when the increased mobility of the joint is demonstrable by pressure on the spinous process.

The unusual disks at the second and third are usually localized by pain in the front of the thigh, the others give pain in the back of the leg

TREATMENT OF RUPTURED DISKS

The treatment of ruptured disks is dictated by the character of the pathologic process. Both the protruding disk and the necrotic interior

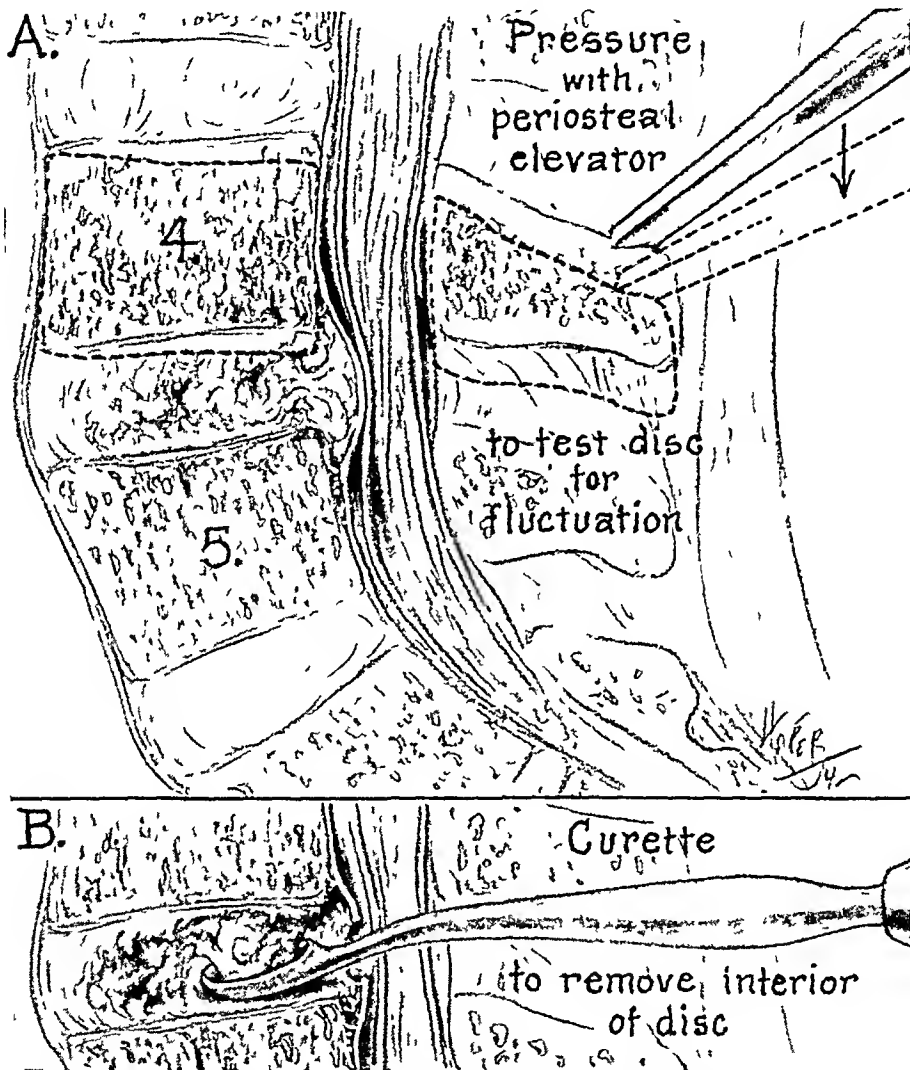


FIG 3—Method of removing the entire interior of the necrotic disk with a curette, this is done painstakingly and thoroughly. After this is accomplished firm fusion of the vertebral surfaces results.

of the disk must be removed. If only the protrusion is removed the back-ache continues and recurrence of sciatica reaches a very high percentage. The cure of a disk requires removal not only of the protrusion but of the entire necrotic interior of the disk. This is done by thorough curettement. If this is carefully done I do not think a disk can recur.

TREATMENT OF THE LATERAL JOINT

When there is excessive movement between the vertebrae, I have opened and curetted the cartilage from the joint on the side of the exposure. This,

INTERVERTEBRAL DISKS

unquestionably, adds to the stabilization but I am not certain that it is necessary. The surfaces of the bodies of the vertebrae after thorough curettement afford such a large area for fusion that fusion of the lateral joints is probably unnecessary. One such joint has been exposed five months later and was absolutely solid, nor was there any movement between the vertebrae which were very loose at the first operation.

CONCERNING SPINAL FUSION OPERATION

At the present time spinal fusions have attained a considerable vogue. The reason for this is that disks have been improperly treated in that the interior of the disk has not been removed. When the entire necrotic disk has been extirpated, firm union occurs between the vertebrae. There is no indication for fusion operations for ruptured disks and every reason for avoiding them. They require three months in a plaster encasement—a severe ordeal on the patient. The disk operation itself requires no encasement and the patient is out of the hospital in ten days to two weeks.

HYPERTROPHIED LIGAMENTUM FLAVUM

Frequently an operator claims the symptoms and signs of a presumed ruptured disk are due to a hypertrophied ligamentum flavum. This is merely a self-satisfying explanation for negative findings. A thickened ligament cannot cause these symptoms. Always there is a disk.

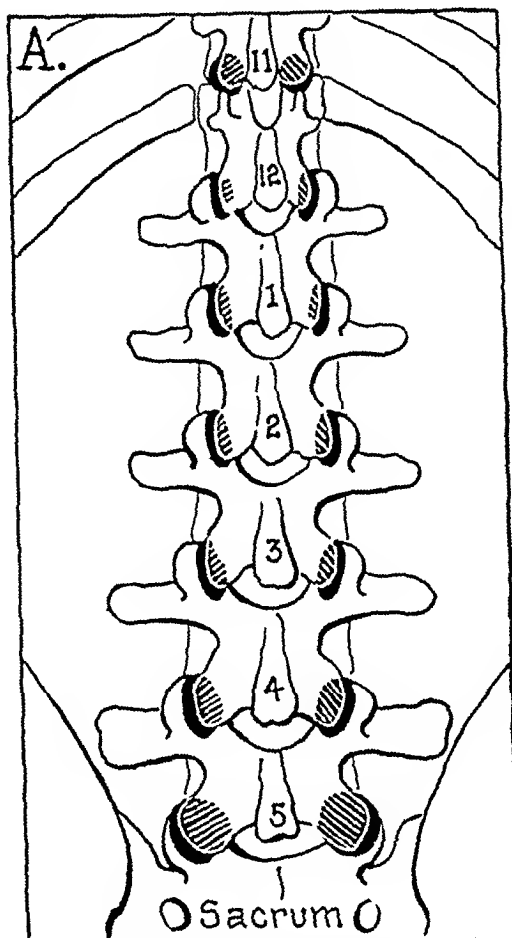


FIG 4—Schematic drawing showing how the lower three, particularly the lower two articular facets shift from the sagittal to an interoposterior direction. This shift is least marked at three, more at four, and most at five. The degree of the shift varies greatly, it may be as much as 90° at the fifth lumbar. This change in the direction of the articular facets allows movement of the spine, but at the same time produces weakness and makes it susceptible to the development of defective intervertebral disks. There may also be marked asymmetry in the two sides.

THE ANATOMIC REASON FOR THE FACT THAT NEARLY ALL DISKS OCCUR AT LUMBAR FOUR AND FIVE

The reason for this concentrated localization of disks to only the fourth and fifth lumbar vertebrae is, I think, explained on an anatomic basis. The planes of the articulations between the vertebrae change markedly at these two sites. Viewing the skeleton from behind it will be seen that the joints of the upper three lumbar vertebrae are parallel to the spinous processes. The plane of the fourth turns 45° and that of the fifth 90° from the horizontal. There are many variations in the degrees of rotation of the joints, the above being the maximum, but always this trend occurs and because of

this, greater movement of the spine—principally flexion and extension but some rotation—is obtained at these two points. The same transverse planes of the articulations occur in the cervical region where maximum movement is obtained. Disks also occur in the cervical region though less frequently because a lesser weight is superimposed.

RESULTS OF DISK OPERATIONS

To date, 506 disks have been operated upon. Always recognizing the importance of treating the interior of the disk, the treatment until recently had been only to break up the interior with an instrument and depend upon the subsequent spontaneous extrusion of the necrotic content through the surgical opening in the posterior ligament. The last 300 disks have been thoroughly curetted during the past year. Of these, there has as yet been no recurrence, but the time interval of one year is too short for comparison. However, I feel that recurrences should now be rare if the treatment is properly done.

The recurrences from the entire series are 25, or nearly five per cent. If the thoroughly curetted joints are excluded the recurrences in the series up to that time would be 14 per cent.

In the last 400 operations a disk has been missed only once—a tumor being responsible. In none of these has contrast media been used.

CONCLUSIONS

(1) Ruptured disks are among the most common lesions coming to surgery.

(2) Spontaneous cures must be very rare, although temporary remissions are the rule.

(3) There are two components of a ruptured disk: (1) The necrotic interior of the disk causing backache, and (2) the protruding portion causing sciatica.

(4) The diagnosis of a disk is made solely upon the signs and symptoms and roentgenograms of the spine. All disks can be diagnosed correctly and found at operation.

(5) Spinal injections of contrast media and spinal punctures are contraindicated, they are unnecessary and they will diagnose only one-third of the total number.

(6) The small (concealed) disks outnumber the markedly protruding ones two to one. They cannot show with any spinal injections of contrast media. It is the recognition of this group that has cleared the whole field of disk lesions. Their recognition at operation is unequivocal.

(7) Two disks in the same patient occur in about 20 per cent of the cases. Very occasionally there is a third disk.

(8) The exposure is unilateral and between the laminae without removal of any bone whatever (Love's operation), or when the interlaminal opening is too small the removal of a small bite of lamina may be necessary.

(9) Mobility of the vertebra, tested by pressure on the spinous process

INTERVERTEBRAL DISKS

will usually determine whether the disk is at the fourth and fifth lumbar (98 per cent are at these two disks), or at both

(10) The entire necrotic content of the interior of the disk should be thoroughly removed with curettes. This is the best insurance against recurrences.

(11) Fusion operations are unnecessary and are contraindicated. Fusion of the vertebrae occurs after removing the necrotic contents of the disk. The articular surfaces can be curetted to induce further fusion in very loose joints, but I doubt that this is necessary.

(12) The reason for the localization of 98 per cent of the lumbar disks through the fourth and fifth lumbar is probably due to a shift in the plane of the articular processes from the horizontal to a transverse direction.

DISCUSSION—DR GILBERT HORRAN (Boston) Doctor Dandy has made such important and significant contributions to neurosurgery, as we all know, that I have some misgivings, as I think anyone would, in disagreeing with him on some of these questions which he has brought up, because he is a person of wide experience, and we all realize how much he has done to bring neurosurgery to the point which it has reached at the present time. As a matter of fact, I do agree with him on some of the points which he has stated here.

In the first place, I think all of us would agree that anything which simplifies diagnosis is important. If we can get away from lumbar punctures or from other types of procedures which are unnecessary, well and good, and insofar as we can, I say, all right.

Second, I would agree that the vast majority of the ruptured intervertebral disks in the lumbar region can be diagnosed by the symptomatology of the patients and the signs which they show. On the other hand, there are the two per cent, or possibly five per cent,—in our experience it is near five per cent—of disks which do not occur between the fourth interspace or the fifth interspace, which one has to account for and which one would like to diagnose more definitely, which I will come to in a moment.

I agree also, that now, there is little or no necessity for iodized oil. We have not used iodized oil at the Lahey Clinic for some years, having substituted oxygen for it and we find, with experience, and with the cooperation of the Roentgenologic Department, that oxygen can be used perfectly well, and you can get comparable pictures to those which you obtain with oil.

I agree with Doctor Dandy about the removal of the interior of these disks. I think it is a very important feature that one must recognize and should aim to get out all the degenerated material that it is possible to obtain.

Again, I would say that, on the whole, fusions are very seldom indicated. We have a rule that after roentgenograms have been taken, if the patients show a very unstable lumbosacral region, with local reaction, irrespective of the disk, that those patients, almost certainly, ought to be fused, because such a fusion would cover a wider area than just the simple fusion which one does undoubtedly obtain by taking out the whole of the disks.

But now it seems to me that, from our experience, certainly, there are a great many patients who do not have the typical symptoms of a disk—the patients who have low back pain without the radiation down the leg in the sciatic area, in whom some form of further diagnostic procedure is necessary to determine whether or not a disk is present.

Furthermore, I would say that if one wants to get as accurate a determination as possible as to where the lesion is before operation—just the same way we use ventriculography, not always to diagnose a tumor but to get a more exact idea of its situation—so we find that the use of a contrast medium is advisable in that type of

case—the case that does not give typical symptoms, as well as to pick up the five per cent of patients who do have disks in other localities

We have found, in addition to the ones in the fourth and fifth spaces, we have had nine out of 250 cases at the lumbar third, five at lumbar second, and two at dorsal twelve, in addition to three tumors, all of which had symptoms of ruptured intervertebral disks, and would not have been picked up without the contrast medium. But, as I say, anything which helps toward greater simplification of this problem is certainly commendable

DR ALBERT KEY (St Louis, Mo) We orthopedic men have been wrestling with low back pains for a long time, and patients with low back pain and with sciatica have gotten well and have stayed well for a long time, again and again

I think that I agree with Doctor Dandy about lipiodol and also air. I do not like lipiodol and I cannot interpret air

When his work first came out about concealed disks, I looked for them, and when I got through I was never sure whether I had made the disk and the cavity or it had been there. I did not realize the point that the nerve was always adherent, so I probably have looked in some normal disks for his concealed disks, and I felt that I had done a little more harm than I had good, and then I fused the spines

Removal of the disk will not result in spinal fusion, that is by bony ankylosis between the bodies of the vertebrae. I think most of us have seen unstable lumbar spines with sclerotic opposing surfaces which caused symptoms

In regard to the posterior fusion which is done by most orthopedic surgeons, we now keep our patients in bed only three weeks, and then let them get up with a belt or a low back brace. My criterion for an operation on the spine is a patient who has had the pain so long or is having so much pain that he justifies a major surgical procedure to get rid of it. Unless he is very markedly disabled and has had it for a long time, I do not think operation is justified. Lots of them get well with manipulations. Witness the popularity of the osteopaths. We have manipulated them long before we had osteopaths. Lots of them get well with rest and support. I think those should be tried first

DR WALTER E DANDY (Baltimore, Md closing) There is very little to add. Doctor Horrax has mentioned the fact that some of these disks occurred at the second and third lumbar interspaces. My criterion for a disk higher than the fourth is that the pain is in the front of the leg instead of the back. In my paper I was emphasizing the pains that occur in the back of the leg and not the front of the leg. If there is any question of its location, it can be determined by pressure upon the spinous processes, if the disk is at the second or third lumbar, there will be increased mobility of the affected vertebra

The answer to the question, when to operate, is when they are having enough pain to seek relief. It must be realized that the complaints will probably recur for the remainder of life, for spontaneous cures must be very rare. There may be long remissions, but any little strain on the back reproduces the pain, and then it usually recurs with greater frequency

I have exposed the site of earlier disk operations several times when the patient returns with a second disk, they are perfectly solid. This results because the whole surfaces have been extirpated, and a fusion of the entire bodies of the vertebrae is inevitable. As I indicated before, if the operation is done in that way, and done properly, I do not think a disk can recur

OBSERVATIONS ON THE DISTRIBUTION OF THE SYMPATHETIC NERVES TO THE PUPIL AND UPPER EXTREMITY AS DETERMINED BY STIMULATION OF THE ANTERIOR ROOTS IN MAN¹

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THE SYMPATHETIC NERVOUS SYSTEM, though nicely diagrammed in anatomical texts, has often been found by the surgeon seeking to effect sympathetic denervation of the extremities, to be apparently anomalous beyond all understanding in its devious origins and ramifications. This has been the case particularly with the upper extremities.

In a patient with Raynaud's disease that had had anterior rhizotomy, T 2 through T 8 on the right and T 3 through T 8 on the left, the observation 13 days after operation that skin galvanic responses were present in both hands led us to investigate further the spinal origin of the preganglionic fibers to the upper extremity in man.

It has been obvious that anatomic dissection does not suffice to indicate the physiologic pathways of the sympathetic nervous system. Neither can the information gained from animal experimentation, even in monkeys, be transposed to man. The contributions of trial surgical procedures of the sympathetic system in man have often been useful but just as often inconclusive and misleading. Witness, for example, the conflicting reports regarding the spinal origin of the preganglionic sympathetic outflow to the upper extremity in man. Gask and Ross¹ (1937) stated that the preganglionic sympathetic fibers for the arm extend from the segmental levels of the cord T 4 to T 9. Foerster² (1939), using the plethysmograph, made observations of vascular changes in the upper extremity on stimulation of anterior nerve roots. He concluded that the preganglionic fibers producing vasoconstriction in the upper extremity exit *via* anterior roots T 3, 4, 5 and 6, and possibly T 7. White and Smithwick³ (1941) gave the levels for preganglionic outflow for the control of blood vessels, sweat glands and erector pilae muscles of the arms as T 2 through T 8. Additional evidence^{4, 5} has been supplied to show that T 2 is the upper segmental level for the preganglionic outflow in man. None of these observations has indicated that the upper level ever extends to the first thoracic segment and there is no uniformity of opinion about the lowest segmental level which may supply the upper extremity.

There has been less interest, though equal uncertainty, over the preganglionic outflow of sympathetic fibers to the pupil. Foerster⁶ obtained homo-

¹ Read by title before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

lateral dilatation of the pupil in man by stimulation of anterior roots C 8, T 1 and T 2 Hyndman and Wolkin⁷ found that in five patients in whom anterior roots T 1 to T 5 were sectioned bilaterally, three patients showed bilateral miosis and ptosis, whereas two showed only unilateral changes

Observations made on laboratory animals, chiefly the cat, dog and monkey, have indicated the variation in segmental levels of sympathetic innervation which may occur in different animals as well as in the observations of different experimenters and emphasized how unreliable are any attempts to commute the findings to man Langley⁸ concluded that the preganglionic outflow to the forelimb in the cat occurs in the fourth to the tenth thoracic nerve roots Ascroft⁹ found in monkeys that the segmental levels were T 3 through T 9 Kuntz, Alexander and Furcolo¹⁰ concluded from experiments with cats and dogs that the "white communicating ramus of the first and lower thoracic nerves include preganglionic fibers which effect synaptic connections with ganglion cells involved in the sympathetic innervation of the upper extremity" Sheehan and Marrazzi¹¹ have determined the preganglionic outflow to the upper extremity in the monkey by recording electrical activity of peripheral nerves during stimulation of anterior nerve roots and concluded that the outflow is limited to roots T 4 through T 8 Kuntz and Dillon¹² using the changes in the extremity recorded by a photo-electric plethysmograph following stimulation of anterior roots, maintain that in cats and monkeys the sympathetic outflow to the upper extremity has its upper level at the first thoracic segment

By recording changes in skin resistance on stimulating the anterior roots Geohagan, *et al*¹³ determined the preganglionic sympathetic outflow to the limbs in cats and monkeys They noted not only the variation from animal to animal but emphasized the difference in segmental levels of outflow that may exist on the two sides in a rhesus monkey Their experiments were performed primarily to establish the validity of a method that could be used in the operating room for defining the origin of preganglionic fibers in man

We^{13, 14} have taken advantage of the opportunity to make observations at the operating table in 18 patients in whom the cervicothoracic region of the spinal cord was exposed for one reason or another The tests were based upon the established fact that sympathetic nerves leave the cord *via* anterior spinal roots and that faradic stimulation of these roots causes sympathetic activity, one effect of which is a change in the electrical resistance of the skin in the area innervated In some cases it was possible to stimulate the lower cervical and upper thoracic roots, in other cases the lower thoracic levels, and in still others the entire thoracic preganglionic sympathetic outflow to the upper extremity

METHOD

The majority of the patients upon whom the observations were made were operated upon for relief of pain, the remainder had Raynaud's disease Ether anesthesia was employed in all, and the preoperative dose of atropine was

limited to 0.0002 Gm hypodermically. Fluids were administered intravenously throughout the operations in an effort to maintain the body's autonomic balance. In a few patients who developed even a moderate degree of shock the changes in skin resistance on stimulation of the roots were found to be unreliable.

A laminectomy was performed and the cord with its roots was exposed after opening the dura. The nerve roots were identified readily by skin markers over vertebral spines whose location was verified by roentgenograms before operation. Additional verification was afforded by postoperative roentgenograms showing the positions of silver clips placed in the dura at the foramina of the nerve roots. When the upper thoracic level of the cord was exposed, anterior root T 1 could easily be distinguished from T 2 not only by the difference in size but by the effects of stimulation—stimulation of the former resulting in muscular contractions in the hand and of the latter in muscular contraction of the back.

The anterior roots to be stimulated were successively isolated and held up on fine glass hooks. It was felt to be relatively certain that no spread of the stimulation occurred either to the cord or to adjacent roots. This was verified in many instances by obtaining sympathetic responses on stimulation of anterior roots after section of corresponding posterior roots or adjacent anterior roots, as well as by stimulation of the distal portions of transected anterior roots. Also, after positive results had been obtained, negative responses resulted when anterior roots were stimulated proximal to the point of crushing. In a number of cases simultaneous observations were made of the skin resistance in each hand and the positive responses were always limited to the side of the stimulation.

Two types of stimulation were employed, one delivered by a thyroton stimulator and the other by a 60-cycle alternating current of about 2 r m s volts measured under load. In the latter method the stimulus was derived from a simplified sine-wave stimulator, to be described later, and this method was found to be more desirable.

The changes in the electrical resistance of the skin of the fingers was utilized as an index of sympathetic activity. It is maintained by some¹⁶ that the lowering of the skin resistance is dependent upon the synchronous development of both vasoconstriction and of sweating, occurring when either of these is present but being abolished when both are absent. Others¹⁷ believe the skin resistance depends largely on sweat gland activity, being high when sweat glands are inactive and low when they are active. However, all agree that the lowering of skin resistance is a reliable indication of sympathetic activity and for our purposes this affords a convenient and reliable method for studying the sympathetic activity in man under the conditions imposed in experimentation at the operating table.

The changes in skin resistance were recorded by means of zinc electrodes fastened by finger stalls to the palmar side of the digits which had been cleaned with normal saline and wetted with saturated zinc sulphate solution. The

other electrode was fastened beneath the skin or to the exposed muscles of the back. In early experiments a Wheatstone bridge circuit was used in such a manner that changes in but one digit could be observed. Later, observations were made by a recorder built by Rahm Instrument Company, according to specifications developed by Geohegan. With this instrument it was possible to record graphically the changes in resistance occurring at two points of the body simultaneously. Thus, if simultaneous changes should occur in both hands following stimulation of the roots of one side such changes would be observed.

When electrodes were placed on various pairs of fingers of one hand it was found that a change in the skin resistance of one was always accompanied by a similar change in the other following stimulation of an anterior root. Thus, the stimulation of any anterior root containing preganglionic fibers to the hand resulted in simultaneous changes in all fingers of that hand and there was no suggestion of segmental innervation. This observation is in keeping with the conclusion of Billingsley and Ranson¹⁸, namely, that the preganglionic fibers of any given spinal nerve root have an extensive connection with the peripheral ganglia.

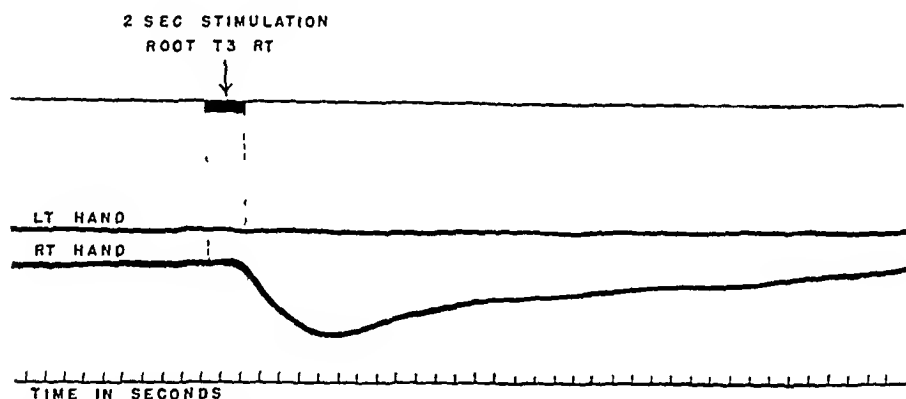


FIG 1—Record of skin resistance in the hands following electrical stimulation of anterior root T₃ on the right. The upper line represents the left hand—the lower the right hand. The downward deflection of the line indicates a decrease in skin resistance.

Unfortunately, stimulation of any of the anterior roots above T₂ causes movement of the extremity and distorts the recording of the skin resistance. However, the form of the wave (Fig 1) and the latent period make it possible to distinguish between muscular movement and decrease in skin resistance. The former begins and ends with the stimulation and the wave fronts are sharp while the latter has a latent period of one to two seconds and the response is gradual and prolonged.

The pupils were observed for dilatation during each stimulation in order to establish the levels of their preganglionic innervation. These observations were possible in only eight of the cases in which the cervicothoracic segments were exposed.

ANTERIOR ROOT STIMULATION

RESULTS

The responses obtained from 16 patients in whom changes in the skin resistance of the hand were observed on stimulation of anterior spinal roots are summarized in Table I

Of the 11 cases in which the highest levels of preganglionic outflow to the hand were investigated, ten showed the uppermost root of outflow to be T 2. In one case (Case 1), T 1 on one side contained preganglionic fibers to the hand and in another (Case 2), T 3 was the uppermost root of innervation on one side. Thus, in these two cases there was a difference in each person of one segment in the highest levels on the two sides.

Of the seven cases in which the lowest levels of preganglionic outflow to the hand were tested, the levels were variously found to be T 7, 8, 9 and 10. In two cases (Cases 12 and 16), there was a difference of one segment in the lowest levels on the two sides in the same person.

TABLE I

SPINAL LEVELS FOR SYMPATHETIC CONTROL
OF UPPER EXTREMITY



















CASE NO	TH I	2	3	4	5	6	7	8	9	10	11
1	LT	+	+	+	+	+					
	RT	0	+	+	+	+					
2	LT	0	+	+	+	+					
	RT	0	0	+	+	+					
3		0	+	+	+	+					
4		0	+	+	+	+					
5		0	+	+	+	+					
6		0	+	+	+	+					
7		0	+	+	+	+	+				
8		0	+	+	+	+	+				
9		0	+	+	+	+	+				
10		0	+	+	+	+	+	+	0	0	
11		0	+	+	+	+	+	+	+	0	
12	LT						+	+	+	0	
	RT						+	+	0	0	
13						+	+	+	+	0	
14						+	+	+	+	0	
15						+	+	+	+	+	0
16	LT						+	+	+	+	0
	RT						+	+	+	0	0

TABLE II

SPINAL LEVELS FOR PUPILLARY CONTROL

CASE NO.	C 8	TH	1	2	3	4	5
1	+	+	+	+	0		
2	0	+	0	0			
3	0	+	0	0			
4	0	+	+	0			
5	0	+	+	0			
6	0	+	+	0			
7	0	+	+	0			
8	0	+	+	+	0		
9	0	+	+	+	+	0	
10	0	+	+	+	+	+	0

In two cases (Cases 10 and 11), the entire extent of the thoracic sympathetic outflow to the hand was examined.

In a few cases there appeared to be some difference quantitatively in the response to stimulation of various roots. Particularly was it noted that the

upper and lowermost roots were likely on stimulation to give a response of less degree than followed stimulation of the roots between. However, this was not a constant finding and the limited observations thus far make it unwise to conclude that these variations are of any significance.

The results of an additional study made in eight of the cases included in Table I and in two additional cases of the dilatation of the homolateral pupil on stimulation of anterior roots, are summarized in Table II. In one case (Case 1), the preganglionic outflow to the pupil was through anterior roots C 8 to T 3. In two cases (Cases 2 and 3), stimulation of root T 1 alone caused pupillary dilatation. In four cases (Cases 4, 5, 6 and 7), anterior roots T 1 and T 2 contained pupillary fibers, in one case (Case 8), it was roots T 1, 2 and 3, and in two cases (Cases 9 and 10), it was roots T 1, 2, 3 and 4.

DISCUSSION

The observations amply demonstrate the great variability in the segmental sympathetic innervation of the upper extremity and the pupil in man—variability not only in different individuals but between the two sides in the same individual.

Such information can be put to practical use in the diagnosis of the levels of lesions involving the cord or the thoracic sympathetic chain. It would explain, for example, the impaired sweating in the upper extremity (and in the face which probably has its innervation below T 1) with preservation of pupillary and palpebral function in the case of a paravertebral tumor (such as a "Pancoast tumor") which paralyzed all ascending components of the thoracic sympathetic chain below the first thoracic ganglion.¹⁹

We attempted to put the information to practical use in the treatment of Raynaud's disease with only partial success as far as total and permanent sympathetic denervation of the extremity is concerned. It was reasoned that the unfavorable late results in some patients, after one of the standard operations on the thoracic sympathetic chain, was probably due to the failure of the operation to prevent regeneration of nerves. The most popular operation, of recent time, has been that proposed by Smithwick,²⁰ in which, extraspinally, the second and third thoracic sympathetic ganglia are freed from their central connections by cutting their rami communicantes and dividing the thoracic chain below the third ganglion. It was hoped that one advantage of dividing the anterior spinal roots which contained sympathetic fibers to the extremity would be to prevent or greatly minimize the possibility of regeneration.

In three cases (Cases 10 and 11 in Chart 1, and one other) all or all but one of the anterior roots on both sides, found by stimulation to possess preganglionic fibers for sympathetic innervation of the hands, were sectioned. The protocol of one of these cases will serve to illustrate what results were encountered.

In a patient with Raynaud's disease the skin temperature of the hands before operation, as recorded by a radiometer in a controlled temperature room at 25°C approximated 23°C in each hand. Block of the left stellate

ganglion with procaine was followed by vascular dilatation in the left hand and a skin temperature as high as 33°C . This demonstrated the ability of the peripheral vessels to dilate when released from vasomotor control. At operation, a lowering of the skin resistance in the hand was produced by stimulation of each of the anterior spinal nerve roots T 2 through T 9 on the left and T 2 through T 8 on the right. The anterior roots from T 2 to T 8 inclusive were cut on each side. Final stimulation of the intact T 9 root on the left still produced a lowering of the skin resistance in the left hand.

Twenty-one days later the skin galvanic reflexes induced by scratching the sole of the foot were absent in the right hand but present in the left. This demonstrated the presence of the remaining preganglionic innervation, presumably through root T 9 on the left side. Skin temperatures of the fingers on the right averaged 33°C and on the left 27°C . We interpret this to mean that the remaining anterior root T 9 on the left was sufficient to maintain the skin temperature 6°C lower in that hand, yet as a result of section of the other anterior roots on the left that hand was 4°C warmer than before operation.

Ten weeks after operation repetition of tests showed that skin galvanic reflexes were now present in both hands and the skin temperature had dropped to about 24°C on the right and 23°C on the left. The right ulnar nerve was blocked with procaine and the temperature rose in the ulnar half of the right hand to about 29°C ; no skin galvanic reflexes were now obtained in this part of the hand. This proves that sympathetic innervation had been reestablished on the right even though we had employed the usual procedure at operation of applying silver clips to the central and distal ends of sectioned roots.

We have assumed that the reestablishment of sympathetic innervation was probably not due to regeneration of cut fibers but possibly to some form of rearrangement or supplementation²¹ of the outflow through roots not found at operation to possess fibers that caused changes in skin resistance when stimulated. However, regeneration of fibers from without into a ganglion may take place.

Thus, in addition to the variability in the segmental extent to which preganglionic fibers have been found present in man, must be added the observation that the interruption of all nerve roots found on stimulation to contain sympathetic fibers to the extremity in a given case may not be sufficient to effect permanent release in that extremity from sympathetic control. While the degree of sympathetic innervation which appears to be reestablished is not sufficient to affect materially in Raynaud's disease the benefits derived from multiple rhizotomy, the failure to cut all the roots originally found to contain preganglionic fibers is another matter. The case reported, in which the lowest root (T 9) was left intact, as well as another case in which the uppermost root (T 2) was spared, demonstrated that relatively little clinical improvement

occurred if but one of the six to nine roots containing preganglionic outflow to the upper extremity was left intact

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SUMMARY AND CONCLUSIONS

Knowledge of the preganglionic sympathetic outflow to the upper extremity and to the pupil in man has been incomplete, largely because it has been deduced by indirect methods or by attempting to commute the experimental observations in laboratory animals

In a series of 18 patients in whom the cervicothoracic region of the spinal cord was exposed the anterior nerve roots have been electrically stimulated and observations made on the changes in the pupil and in diminished skin resistance in the hands

Observations on changes in the pupil were made in ten patients and showed that the sympathetic innervation traveled through one or more roots and between the levels of C 8 and T 4

In 16 patients in whom the levels of preganglionic innervation to the hand were investigated it was found that there was variation in the upper and lower levels within the limits of T 1 and T 10. This variation occurred from one individual to another, and on the two sides in the same individual

In patients with Raynaud's disease division of all but one of the anterior roots found to possess preganglionic fibers to the hand resulted in preservation of much of the sympathetic effects in all parts of the hand and in but partial clinical improvement

It was also found that after division of all anterior roots containing sympathetic fibers to the hand there was return of some sympathetic activity in that extremity by the tenth week. This is interpreted as possibly indicating a functional reorganization through other pathways

The observations emphasize the necessity for recognizing the variability in the levels of sympathetic control to the upper extremity and pupil in man

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ACUTE PUTRID ABSCESS OF THE LUNG*

VII RELATIONSHIP OF THE TECHNIC OF THE ONE-STAGE OPERATION TO RESULTS

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AT THE PRESENT TIME there appears to be rather general agreement with the views we have set forth repeatedly concerning the desirability of operating upon putrid pulmonary abscess in its acute stage. There is no general agreement however, on the operative technic to be employed for acute abscess. There is advocated a variety of procedures such as the two-stage operation, cautery incision, intubation of the abscess cavity, partial or complete lobectomy, *etc*. The advantages (or disadvantages) of these operative techniques cannot be analyzed logically because authors usually do not present arguments in favor of the procedures which they advocate. Thus, the reader is constrained to conclude that reported operative mortalities are chiefly or usually referable to an advanced or complicated stage of the disease which existed at the time of operation. Indeed, there is a tendency to classify acute abscess into "complicated" with higher, and "simple" with lower operative mortality. We propose (1) to present briefly the basis for the one-stage operation which has been employed in our clinic since 1925, (2) to describe the technic of the one-stage operation, and (3) to show that the operative mortality and morbidity as well as the late results of operation are related almost invariably to the operation and not to the disease.

(1) BASIS FOR ONE-STAGE OPERATION

The one-stage operation is based on the knowledge of the pathology of acute putrid pulmonary abscess and on the fact that anerobiasis plays an important (preponderant?) role in the infection. The details of the pathology have been described elsewhere,^{1,2} In brief, an acute putrid abscess usually is solitary, of substantial proportions, superficially situated within the lung, and overlaid by well-developed visceroparietal agglutinating adhesions. By virtue of early liquefaction within the segmental area of gangrenous bronchopneumonia (which is the initial lesion) the abscess presenting the foregoing features exists as such within a week or ten days of the onset. The shell of lung overlying the abscess generally is thin, compressed, and avascular even in the earliest stages. Rare exceptions to the usual presence of agglutinating visceroparietal adhesions are to be found in abscesses facing fissures, the diaphragm, or the mediastinum. Under such circumstances overlying adhesions also exist but may be local and not visceroparietal. These are the unusual instances in which the free pleural space may have to be traversed.

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in order to enter the abscess. All other abscesses can be opened at a one-stage operation without traversing the free pleura.

Precise roentgenologic localization of the abscess is an essential element of the one-stage operation and can, indeed, be regarded as the cornerstone upon which the one-stage procedure is based. Further reference to the subject will be made in the description of operative technic, but we may say here that, since the *only* means of knowing the site of contact of the abscess with the thoracic parietes (the site of adhesions) is precise roentgenography, the omission of exact roentgenologic localization of the abscess precludes the performance of a safe one-stage operation. Technically satisfactory roentgenograms cannot err, hence entry of the free pleural space at the time of operation (with the rare exceptions noted above) must represent an error in interpretation of films.

Even though a primary anaerobic origin of putrid pulmonary abscess has not been established unequivocally there can be no question as to the importance of the anaerobic factor. The latter, according to all our experience, can be rapidly and completely eliminated only by liberal unroofing of the abscess. Thus, unroofing, not simple drainage, is an essential feature of the one-stage operation, and its performance under good vision usually can be carried out only at the primary operation.

(2) TECHNIC OF THE ONE-STAGE OPERATION

Since the technic of the one-stage operation is based upon precise roentgenologic localization, some consideration of the methods of localization is warranted. A study of properly taken postero-anterior, lateral and oblique films supplies the necessary information as to the situation of the abscess and its site of contact with the thoracic parietes. But it is at this point that the possibility, or at times the probability, of error begins. While it is true that in a few situations (thin individuals in which rib counting can be accurate, paravertebral abscesses in certain situations, anterior abscesses in the upper chest, *etc.*) the chances for error in localization are minimal, a margin of error always exists, and increases under a variety of circumstances (small abscesses, abscesses situated toward the axilla, abscesses in heavy-set individuals, abscesses partially or completely facing fissures, *etc.*) This gap between the true portrayal in roentgenograms and the possible, or probably, incorrect approach by the surgeon is completely bridged by the method of spot localization introduced by Rabin.³ To outline the method briefly. After study of the films and fluoroscopy shortly before operation the assumed point of contact of the pulmonary abscess with the thoracic parietes is determined. The intercostal musculature at this point is injected with a small amount of a mixture of iodized oil and methylene blue. A new set of roentgenograms is taken. There is then revealed the exact relationship of the "spot" (of iodized oil) to the abscess. It may be directly over the abscess or as much as an inch away. The stain of methylene blue, which is in the same situation as the iodized oil, is exposed at operation. After it is revealed by an incision

down to the intercostal musculature one is in position to extend the exposure in the appropriate direction, and to the appropriate extent, in accordance with the relationship of the "spot" to the place of contact of abscess with chest wall. This ingenious method has made possible the precise operative exposure of many abscesses. It has failed in a few instances which, however, were the result of failure to inject properly the intercostal musculature. During the past two years the method has been employed in most operative cases, for we have learned that at times we may be as much as one rib off even in apparently simple cases. Local anesthesia is employed in practically all cases, except in young children. The subperiosteal removal of a two- or three-inch segment of one rib usually suffices. The excision of a section of an additional rib may be required for an unusually large abscess or, more often, because the primary exposure was not quite correct. As has been stated, adhesions are well-developed over the abscess at a very early stage. Other than in children, in whom adhesions tend to be rather tenuous the absence of adequate visceroparietal agglutinating adhesions comprises almost absolute evidence (exceptions already noted) of an incorrect exposure for an acute abscess. (In the subacute or chronic stages adhesions often are less firm and edematous.) In recent years, we have often noted in the operative field the actual prominence and elastic feel of an abscess through presenting adhesions. We ascribe this frequent finding to greater precision in operative exposure, chiefly referable to Rabin's spot localization. The adhesions are delicately traversed over a small area down to adherent lung. This is done in order to be sure that the free pleural space is completely sealed off.

The abscess now is aspirated with a short aspirating needle which should be of a sufficient diameter to permit the withdrawal of thick, inspissated material. It cannot be too strongly emphasized that the abscess is superficially situated in the great preponderance of cases and that usually only a thin shell of lung is to be traversed in order to encounter foul air or pus. Here again, the site of aspiration is almost certainly incorrect if the abscess is found at a depth of more than a half inch. The overlying shell of compressed, avascular lung usually is about a quarter-inch in thickness and can be incised with impunity. The aspirating needle being held in place, we follow with a cutting grooved director and cutting scissors (Touroff¹), urging the patient to avoid coughing at this stage. Once a clean entry into the abscess cavity is obtained the patient is permitted to cough if he wishes, and the contents of the abscess are evacuated by suction. Under full visualization the shell of lung over the abscess is generously excised within the limits of pleural adhesions. Bleeding from a pulmonary vessel, which is uncommon, can be controlled by a hemostatic suture. The result of the excision of the lid of pulmonary tissue should be an opening into the abscess almost as large as the cavity. Only in cases of large abscesses or in exceptional instances of limited pleural adhesions will the opening be appreciably smaller. An essential part of the operation is the unroofing of recesses in the abscess cavity,

which may at times require the incision of a thicker layer of pulmonary tissue, with occasional hemorrhage. Recesses are not rare, especially in cases operated upon in the fourth and fifth weeks, and their non- or incomplete unroofing at operation may result in persistence of the manifestations of pulmonary abscess. The disclosure of one or more bronchial fistulae is clear evidence that the main chamber of the abscess has been opened. A fistula often can be demonstrated by having the patient cough or strain. However, the orifices which are invariably present may be obstructed by blood clot or pus and, as a result, cannot be revealed at operation. The operation is terminated by gauze tamponade of the cavity. All recesses, as well as the main cavity, must be widely packed in order to avoid leaving behind foci of anaerobic infection. This essential step is facilitated by the use of narrow ribbon retractors and a sterile light placed into the cavity. Gauze strips are first packed into the recesses and then the main cavity is packed by superimposed strips of gauze. Tamponade is a correct term for the gauze pack of the cavity for the purpose is to avoid a collapse and consequent shutting off of any part of the abscess. An otherwise satisfactory operation may result in failure (so-called recurrence) if the precaution of wide packing of the abscess is not taken.

The entry of the free pleural space adjacent to adhesions, which usually is referable to an error in localization (at times to violent coughing or straining during operation) requires painstaking attention in order to avoid a possibly fatal putrid empyema. Placing a packing over a small opening into the free pleura does not suffice. When the one-stage operation is performed it is best to convert a small pleural opening into a larger one, for the lung adjacent to the abscess can then be broadly sutured to the thoracic musculature. The sutures should take deep bites into normal pulmonary tissue and there should be no pleural gaps after they have been tied. There should, however, be no tension on these sutures. After a gauze pack is placed and held in place over the suture line, the usual steps of the one-stage operation can be safely proceeded with. If, however, the pleural entry is not cared for by suture of the lung to the thoracic parietes a two-stage operation probably is safer. Thus, emphasis is placed on the desirability of recognition, frank acceptance, and fully adequate management of inadvertent entry of the free pleural space. Reference will be made later to the results of such management.

As has been stated, cases of pulmonary abscess in which adhesions are local and not visceroparietal (abscesses facing the fissure *etc.*) are rare. Their satisfactory management by a one-stage operation at times presents difficulties, and, therefore, raises the question as to the desirability of a two-stage operation in such cases. Indeed, it will be noted that the fatal issue of one of our cases was in part referable to infection following a one-stage procedure. On the other hand, delay in opening a putrid abscess which goes with a two-stage operation invites serious and possibly fatal complications — spread of the abscess, spill-over infection to other pulmonary areas, pleural

contamination, difficulties in finding or in adequately unroofing the abscess at the second stage. The technic of the one-stage operation for the abscess in question should consist essentially of a liberal opening of the free pleura and the broad approximation by sutures of normal lung (adjacent to the abscess) to the thoracic parietes. For example, an abscess of the lower lobe faces the midportion of the long fissure and only local adhesions exist. The operative approach has been through the midaxilla and the free pleural space has been widely opened. Adhesions of the upper lobe to the interlobar surface of the abscess are freed in order to release enough of the free margin of the lobe for suture to the thoracic parietes. After this has been accomplished the surface of the lower lobe beyond the abscess is sutured to the musculature of the chest wall. The free pleural space is thus sealed off. After a strip of gauze is laid and held over the suture line the entry and unroofing of the abscess is proceeded with. A fortunately rarer abscess presenting a more difficult problem is one facing the diaphragm or pericardium. An extensive surgical procedure may be required. Thus, it may be necessary to expose and draw out of the wound much of the free border of the lower lobe and suture it to the thoracic parietes before proceeding with the unroofing of the abscess. The latter may be situated at a great depth and special precautions may be required in order to avoid pleural contamination.

Reference will be made shortly to the results of the one-stage operation for cases in which visceroparietal adhesions were absent.

Some reference must be made to postoperative management, for it is related directly to the operative procedure. The expectoration of foul pus (usually present before operation) should stop promptly after operation. Its persistence is evidence of an inadequate procedure. Since we are concerned here with the relationship of operative technic to results it will suffice to point out that the inadequate operation must be followed by an adequate one if cure is to be achieved.

Assuming that the postoperative course and roentgenograms indicate that the pulmonary abscess has been adequately cared for, the problem of interest here is that of wound closure. We have learned that after an adequate operation the premature closure of an abscess cavity may, and often will, lead to recurrence of the manifestations of pulmonary abscess. The reason appears to lie in a tendency towards the persistence of anaerobic infection in the wounds. Therefore, the wound is kept open and the bronchial fistula maintained until the patient is free from cough and expectoration and roentgenograms establish the absence of pulmonary infiltration about the lesion.² Failure to adhere to these standards has led to recurrence of the pulmonary abscess, as will be recorded in some cases in our series.

A special problem exists in the case of unusually large pulmonary cavities which may be left after operation for large abscesses. The tendency toward early healing exists as in other cavities and must also be combatted. In addition, however, the closure of a large cavity may leave within the lung a considerable dead space. The potential danger of late infection within such

a dead space must be borne in mind, and we shall report one unfortunate case which will illustrate the point. We have employed free transplantation of fat in order to solve the problem of the large postoperative cavity which will not close, or which should not be permitted to close, because of the resultant large dead space⁵. On the whole, the results have been satisfactory although at times some dead space appears to remain (judging from the roentgenograms) when the fat graft becomes absorbed either as a whole or in part. The method is mentioned because we are concerned here with the question of the relationship of the technic of operation to the result.

(3) CAUSES OF OPERATIVE MORTALITY AND MORBIDITY

It will now be shown that the operative mortality and morbidity, as well as the late results of operation, are directly related to the technic of operation (and postoperative management) in the great preponderance of cases. Conversely, it will be shown that they are rarely related to the severity or extent of the disease. The following analysis can be regarded as timely because of the present-day tendency to ascribe operative mortality to the existence of "complicated" forms of the disease as well as to relate both early and late recurrences to the disease and not to the operation.

The one-stage operation which was performed in the great majority of our cases has, of course, been improved upon over a period of years. Thus, a few of the untoward results in our early experience almost certainly would not be seen at the present time. However, almost all cases have been operated upon in accordance with the principles and technic of operation which have been set forth, and all will be placed in the one category.

The series comprises 162 patients who were operated upon for acute putrid pulmonary abscess. There was no selection of cases, and many severe (hyperacute) cases are included⁶. There were four deaths, a mortality of 2.47 per cent. This mortality in an unselected large series in itself comprises evidence that death after operation can be rarely ascribable to the disease. The causes of death and the autopsy findings in the fatal cases have been detailed elsewhere⁷. Here, it should be pointed out that in three of the four cases the fatal issue was related, in whole or in part, to infection consequent upon errors in operative technic. In only one case, unique in our experience, in which a septic course continued unabated after a satisfactory operation, is death ascribable to the disease.

Turning now to the interval and end-results, it can be said, at once, that complications were few and that cure (in the sense of permanent freedom from symptoms and negative roentgenograms) was achieved in the great majority of cases. However, we are concerned particularly with complications and untoward sequelae in order to estimate their relationship to the operation.

Whether or not the free pleural space was opened at the one-stage operation postoperative suppurative pleuritis was extremely rare. It took place in one of the four fatal cases. There were two other instances in which empyema

tollowed inadvertent entry of the pleura early in our experience. They comprise errors in technic. Of special interest is the fact that there was not a single instance of pleural infection amongst all the cases (more than a dozen) in which the free pleural space was entered intentionally at the one-stage operation.

Reference should next be made to the small but important group of cases in which secondary operations were performed usually within a short time of the primary operation. The operations were required either for the enlargement of the existing opening into an abscess or for the unroofing of an adjacent abscess. In either case, the secondary operations are referable to errors in technic and not to the disease. Either the abscess was not adequately unroofed because of too limited adhesions or a recess or pathway leading to an adjacent cavity was not fully laid open. In two cases the results were unfortunate because the spread of infection made necessary repeated operations before a satisfactory result was obtained. Indeed, a chronic abscess ensued in one of them requiring prolonged treatment before cure was achieved. These two cases represent those exceptional instances in which overlying adhesions are not sufficiently widespread for adequate unroofing. The latter is an essential step of the one-stage operation, as already stated. Accordingly, it would have been better technic in the two cases to have opened the free pleura adjacent to the existing adhesions and to have approximated the lung around the abscess to the thoracic parietes over a sufficiently broad area for adequate unroofing of the abscess. Emphasis should be placed on the rarity of limited or delicate adhesions over the abscess. Such adhesions almost always point away from and not towards the site of contact of the abscess with the parietes.

The few instances of failure to recognize at operation a pathway to an adjacent locule (bilocular or even trilocular abscesses are not rare in the acute state of the disease) is strictly speaking referable to an error in roentgenologic interpretation and not to an error in technic. In any event, the secondary operation, which will almost certainly be required in order to achieve a cure, cannot be referable to the disease. Furthermore, purulent discharge from the wound and a few or many of the symptoms of pulmonary abscess which will almost certainly persist if the secondary operation is not performed, surely cannot be ascribed to the disease.

Secondary operations, consisting in laying open the original abscess cavity, were required in several cases because of premature closure of the wound. The intimate relationship between operative technic for and post-operative wound management of acute putrid pulmonary abscess has been emphasized. In a sense, therefore, this group of cases of secondary operations, due to recurrence of symptoms following premature wound closure, is ascribable to errors in technic. Such recurrences cannot be related to the disease. Nor can cases be so related when, after the patient leaves the hospital symptom-free after an adequate operation and subsequently the wound begins to discharge foul (or nonfoul) pus, fever returns, and symptoms

suggestive of recurrence of the abscess set in. As a practical matter, it can be said that meticulous attention to dressings following readmission of such cases usually will lead to the subsidence of all manifestations within a few days.

The operative technic for perforated putrid pulmonary abscess has a very direct bearing on the result. We are concerned solely with the pulmonary abscess of substantial proportions in which the clinical manifestations are essentially those of the abscess. Thus, there is the combined problem (according to the view we hold) of draining the pleural infection and unroofing the abscess even though a perforation, of sorts, exists (only rarely will the spontaneous perforation provide adequate unroofing of the abscess). There were several instances in which we believed patients to be too ill to withstand both wide drainage of the pleural infection and adequate unroofing of the abscess. In all of them secondary operations were required because of persistence or recurrence of the symptoms of pulmonary abscess. All these cases went on to cure but must be termed instances of inadequate technic at the primary operation. Similarly there were a few instances in which the pleural infection was not fully drained at the primary operation and subsequent thoractomy was required.

Finally, the relationship of the operative technic to late results requires consideration. A follow-up of all our cases, often over many years, has established the fact that permanent cure followed the described one-stage operation. Not all patients have survived, however. Death has been due to a variety of unrelated causes such as cancer of the stomach or of the bladder. In almost all these cases an autopsy was obtained revealing complete healing of the abscess and, thereby, providing incontrovertible proof of the relationship of the operative procedure to the result. There was another smaller group of cases in which autopsies made possible a complete study of the results of the one-stage operation. These were patients with chronic pulmonary abscess, operated upon for acute spill-over pulmonary abscess, who died subsequently from the effects of the chronic lesion. The post-mortem examination in these cases revealed the same satisfactory findings in the operative field of the acute abscess as in the patients who died of unrelated causes. There are also several patients who are well, or improved, following operation for acute spill-over abscess complicating chronic abscess. In these the evidence obtained from roentgenograms indicates cure of the acute abscess. There also was a unique case of a spill-over acute abscess from an acute abscess in the opposite lung. Both abscesses were operated upon at the one sitting, and both are healed according to strict criteria.⁸

A late death calls attention to a problem which has not been solved by the technic of the one-stage operation, namely, the occasional persistence of a residual dead space following the operation for unusually large abscesses. We have described our efforts to prevent such residual spaces, including the transplantation of fat. The series of events in the fatal case was as follows. A one-stage operation was performed for an unusually large abscess of the

upper lobe. The postoperative course was entirely satisfactory. The residual cavity was soon clean. Because of its great size healing appeared unlikely. Accordingly, a free fat graft was implanted. Infection supervened, probably because of the unusual size of the graft, the fat masses were removed. The wound healed after five months and remained healed for three years of follow-up. Throughout this period the patient remained entirely well but there persisted in all films an area of rarefaction. The patient came under hospital observation six months later, with the history of a lung abscess of short duration. At operation, there was considerable difficulty in disclosing the abscess, which was finally found in the old dead space only after the free pleura had been entered. A putrid empyema developed which was drained. Death occurred, however, from the results of this infection and from cardiac failure. It was impossible to determine the duration of the pulmonary abscess. Since it occurred precisely at the site of the old lesion, it can be assumed that a low-grade infection existed which was lighted up by some undetermined cause. This assumption appears more likely than that of a new abscess. Accordingly, the case can be classified as being related to the technic of operation or postoperative care. There are several other patients who have been entirely well for years but who bear areas of rarefaction following operation for unusually large abscesses. Follow-up of these cases cannot be permitted to close, for it is conceivable that in other cases, too, late infection in the dead space may supervene.

Although this communication is concerned with the relationship of the technic of operation to the results in cases of acute putrid pulmonary abscess it may not be amiss, in closing, to call attention to the fact that excellent results also have been achieved with the one-stage operation for cases of acute nonputrid pulmonary abscess. Since operation is more rarely indicated for nonputrid abscess, only 22 cases have been operated upon. All recovered, and the follow-up has established the existence of lasting cure in all.

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THE CHOICE OF OPERATION FOR DELAYED AND NONUNION OF LONG BONES*

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WHEN A FRACTURE of a long bone fails to unite after a sufficient interval of time, operative intervention is usually indicated. The object is to provide extra bone for the bridging of gaps, filling of defects and increasing stability, and to stimulate sufficient osteogenesis to result in bony union and to immobilize the fragments in a satisfactory position until union occurs. Other things being equal, the sooner the condition is recognized and treated the better the chance of success and the less the time lost by the patient. Consequently, early recognition of impending nonunion and decision on the part of the surgeon is advisable. However, he should avoid subjecting a patient to an unnecessary operation.

The decision when to advise operative interference may be relatively simple in a case with obvious interposition of soft parts or where several months or more have elapsed since the injury, or it may be very difficult in a borderline case, and the surgeon may err in either direction. Recently, I advised multiple drilling of a fractured tibia which had been treated by the two-pin method for eight weeks and then a plaster encasement for six weeks. There was slight distraction of the fragments and false motion on lateral strain. The patient refused the operation, and four months later union was not firm and the man is not working. This leg may unite eventually under conservative treatment, but I believe that the advice was sound and a relatively simple operation might have saved the patient months of disability.

A few years ago I would have waited until nonunion was unquestionable before advising operative intervention. This was because of the danger of infection. Now this danger is greatly lessened by implanting sulfonamide powder in the clean operative wound. Consequently, operations for nonunion are undertaken much earlier and many patients are saved months of disability and obtain better limbs than would be possible if operations were postponed until permanent nonunion was present. In addition to the sulfonamide in the wound, which I now use routinely in all operations, the patient is given sulfathiazole or sulfadiazine by mouth (one Gm every six hours) for one or two days before and three or four days after the operation if the nonunion is present in a bone which has been infected during the preceding year.

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Now that operations for nonunion are performed earlier than in the past, the choice of operative procedure is broadened. In some instances the fragments are firmly held in good position and osteogenic stimulus is needed, in others internal fixation is necessary, and in a third group extra bone is indicated for filling defects or increasing the strength of the bone. The surgeon should choose the simplest operation which reasonably may be expected to yield a satisfactory result, and he should leave as little foreign material as possible in the wound. With the use of stainless steel and vitallium this is less true than in the past, but still it is advisable to use as little metallic internal fixation as possible, and this is especially true in bones which have been infected and in subcutaneous areas. Likewise, the simpler procedures are less apt to be followed by postoperative complications.

In the order of their complexity the operations which are most useful are (1) Multiple drilling of the fragments, (2) open reduction and internal fixation, with or without multiple drilling of the fragments, (3) step-cut operations, and (4) various types of bone grafts, with or without other internal fixation. Each has its own sphere of usefulness and all should be followed by adequate external fixation—usually a plaster encasement.

1 Multiple Drilling—This is useful in fractures where the ends of the fragments are in satisfactory position and are firmly bound together by dense fibrous tissue which may or may not contain cartilage. If the fragments are not in close contact or if they are bound together loosely so that they can be angulated easily or moved upon one another the operation cannot be expected to result in union. The procedure is especially recommended for oblique or spiral fractures because of the larger area exposed for drilling, but it seems to work equally well in transverse fractures provided the ends of the bones are in good position and are firmly fixed to one another by fibrous tissue or cartilage.

The drilling may be done subcutaneously through small stab incisions or under direct vision after exposing the line of fracture. About six years ago I drilled a simple fracture of the tibia subcutaneously and the operation was followed by a severe infection and extensive sequestration which necessitated two subsequent operations before satisfactory healing was obtained. Consequently, I now expose the fracture site and drill the bones under direct vision. Drills varying from $\frac{3}{32}$ to $\frac{5}{16}$ of an inch in diameter are used and several holes are drilled obliquely across the fracture line from each side and a few through the cortex near the end of each fragment, care being taken not to break up completely the fibrous union. The size of the drill varies directly with the size of the bone.

The wound is closed and the limb immobilized in a plaster encasement and treated as one would a simple fracture in the same location. Firm union may be expected in from six to eight weeks.

2 Open Reduction and Internal Fixation—This procedure is useful in relatively recent fractures (from two to three months old) in which the

ends of the fragments are approximately normal in density. In such fractures interposition of soft parts or incomplete reduction or improper immobilization may account for the lack of union. If the ends of the fragments are sclerotic or atrophic or if they have been maintained in satisfactory position by either internal or external fixation over a sufficiently long period and have shown no evidence of bony union, it is probable that open reduction and internal fixation will fail and a bone graft is indicated.

At operation, the ends of the fragments are exposed and their margins



FIG 1.—Left: Humerus with muscle interposition ten weeks after injury. Right: Same after reduction, freshening of ends, internal fixation and multiple drilling. Immobilized in a "hanging cast" for eight weeks, then active exercise until solid.

are freshened by pinching off the surface layer with rongeurs. The marrow canal of each fragment is opened and the fracture is then reduced and immobilized with noncorrosive wire or screws or a plate if necessary (Fig 5). If large loose fragments are present they may be used as bone plates or splints (Fig 1). No more metal than necessary should be used, but the fixation should be as rigid as possible. After fixation is complete a few small drill-holes should be made across the fracture line and near the ends of the fragments. The wound is closed and the limb immobilized in a plaster encasement and treated as would be a simple fracture in the

same location Union may be expected to be somewhat slower than normal (eight to twelve weeks)

3 The Step-cut Operation—In oblique or transverse fractures of the upper extremity, where a moderate amount of shortening is not very objectionable and which have not united after a reasonable length of time and where the bone ends are in fairly good condition, the step-cut operation



FIG 2—Left Humerus with nonunion nine months after injury, with radial nerve paralysis. Right Same after step cut operation and neurolysis of the radial nerve. Immobilized in a hanging cast¹ for eight weeks, then active exercise. The large loose fragment was removed.

offers a better chance of union than does the simpler open reduction and internal fixation. If the ends of the fragments are markedly sclerotic or atrophied the operation should not be used as it will probably fail to result in union.

At operation, the ends of the fragments are delivered into the wound

and the ends excised, preferably with a saw. Then, a small hole is drilled transversely across each fragment about one inch from the end and, with a saw, a step-cut is made in the end of each fragment to form a tongue including a little more than half of the diameter of the bone. The step-cuts are on opposite sides so that when the ends are pushed together and fastened by two noncorrosive screws placed at different angles they form a fairly stable union (Fig. 2). If necessary the marrow canals are opened before the step-cuts are made and drill-holes are made in the bone near the step-cut. Drilling of the ends of the fragments is usually omitted as it would weaken the bone which is only half its normal thickness. A few bone chips or splinters from the excised bone are placed around the fracture and the wound is closed. The limb is immobilized in a plaster encasement and treated as would be a simple fracture in the same location. Union may be expected in about the normal time (six to ten weeks).

4 Bone Grafting Operations

—Bone grafting operations are used in those instances where it is believed that there is a probability that the simpler procedures mentioned above will not be successful. This is because the use of a bone graft usually increases the gravity of the operation about one-third. It is assumed that the graft is to be an autogenous graft because, while various substitutes for the autogenous graft have been used, I do not believe that any of them actually stimulate osteogenesis. Consequently, if a graft is indicated it should be an autogenous graft. This necessitates a lengthening of the original incision or a second incision.

In many instances in fractures of the leg the graft can be removed from the fractured bone, and I have seen no evidence that this decreases the probability of union of the fracture, and if the operation is on the lower extremity this offers the advantage that the opposite sound leg is not



FIG. 3—Anteroposterior and lateral views of tibia fractured when the patient fell from a high curb. A large graft had been removed two months before the injury. This fracture healed slowly.

temporarily crippled or weakened. That this weakening of the sound leg is an actual hazard if a large graft is removed is evidenced by Figure 3. This leg was fractured by relatively slight violence about two months after the operation, and took longer to heal than did the opposite leg which

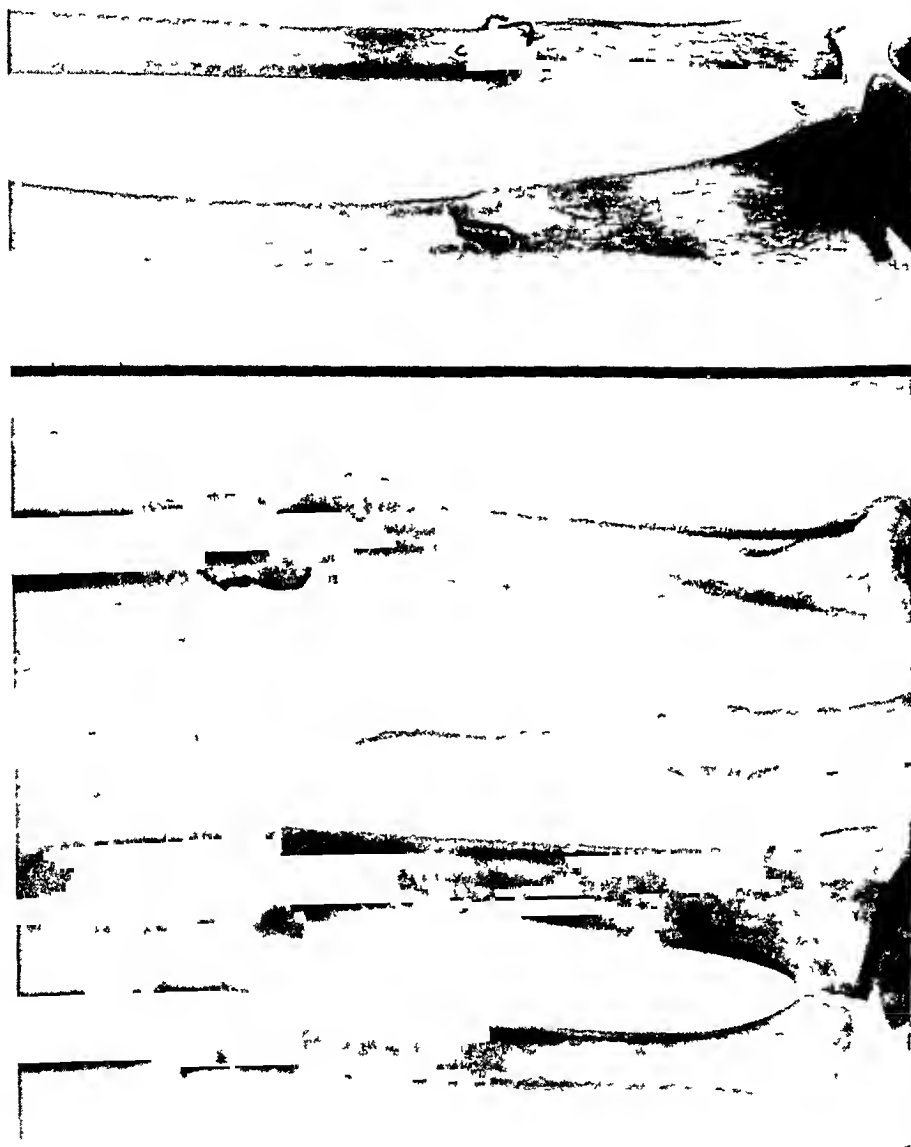


FIG. 4—Top: Radius and ulna reduced, wired and drilled six weeks after the injury. A previous open reduction had failed to maintain position. Below: Radius and ulna five months after fracture. A previous open reduction and wiring of fragments had failed to secure union. Intramedullary and splinter grafts and cancellous bone in each and ulnar fragments held by wire. Immobilized in a plaster encasement for ten weeks.

had been grafted (Fig. 8). This in spite of the fact that spicules of bone had been curled up from both margins of the defect to hasten the filling in my bone of the defect created by removal of the graft.

Notwithstanding the fact that the use of a bone graft increases the

gravity of the operation it will be found that a graft is indicated in most instances where more than three months have elapsed since the injury. The principal exceptions are fractures suitable for step-cut operations or multiple drilling.

Source and Type of Graft—If it is not feasible to remove the graft from the broken bone adjacent to the field of operation, it must be removed from some other bone. The tibia is usually chosen because it presents a large flat subcutaneous surface from which the graft can be cut with a

FIG 5

FIG 6



FIG 5—Left: Nonunion of humerus after three operations. The radial nerve was then sutured and a step cut operation was performed by the author, but still the bone did not unite. Right: Same after an intramedullary graft and wire loop with splinter grafts and cancellous bone. Union was quite firm after eight weeks in a "hanging cast."

FIG 6—Failure of an autogenous intramedullary peg for nonunion of the humerus, the remains of which can be seen in the marrow canal. A wire loop might have made the difference between union and failure.

motor saw with relative ease. If only cancellous bone is needed this is best removed from the ilium. In unusual instances where an extensive defect is to be bridged, as much of the shaft of the fibula as desired may be excised without causing serious disability in the leg.

In deciding upon the type of graft to be used in a given case, the functions which the graft is to perform must be considered. Compact bone is strong and also has considerable osteogenic properties. Consequently, it is the type of bone most frequently used, and this is especially true where it is desirable that the graft provide some internal fixation. Cancellous bone, bone chips and shivers and osteoperiosteal grafts have more osteogenic

power, but offer little in the way of fixation. They are most useful in operations for arthrodesis and in filling defects or in combination with some form of internal fixation (plates, screws or wires, or as adjuncts to cortical bone grafts).

It having been decided that a bone graft is indicated, the surgeon must decide what type of graft will most satisfactorily solve the problems presented by the particular fracture to be operated upon. If the graft is to furnish internal fixation it should be of cortical bone and may be of the massive onlay type of Campbell¹ or Henderson,² the inlay or the wedge graft of Albee,³ the medullary inlay of Buchanan,⁴ the double onlay of Boyd,⁵ the intramedullary graft of Ryerson,⁶ or the massive sliding graft of Gill.⁷ All of these are useful in bridging defects in the bone.

If internal fixation is not to be furnished by the graft, one may use the splint graft of Phemister,⁸ the multiple barrel stave grafts of Steel,⁹ the cancellous bone grafts from the ilium of Abbott,¹⁰ the osteoperiosteal grafts of Ollier or small slivers of cortical bone or bone chips and fragments of cancellous bone and endosteal bone placed around the line of the fracture and between the ends of the fragments. This group is especially useful when combined with internal fixation by noncompressive metal plates, wire or screws, and in instances where metal is to be avoided because of recent infection or infection present at the time of the operation. They are also useful adjuncts to multiple drilling operations.

Technic—In the usual case of nonunion of a large bone of several months duration with sclerosis of the bone ends and a pseudarthrosis or flexible fibrous union, I prefer the massive onlay graft of Campbell or Henderson, but use the entire cortex of the bone, do not prepare a flat bed, and fix the graft with metal screws (Key¹¹). In preparing the site for the graft the ends of the fragments are exposed subperiosteally and the dense fibrous tissue around and between the fragments and the adjacent sclerotic bone is excised. The marrow canal of each fragment is opened by removal of the plug of eburnated bone which occludes it. The fragments are then remodeled and placed in a satisfactory position and if possible an end-to-end apposition is obtained.

It is often stated that as little periosteum as possible should be removed from the ends of the fragments, but I have exposed the ends rather generously and have not seen that it did any harm as fairly prompt union has always followed this operation. With the exception of congenital fractures my failures have occurred in patients in whom I have used some other operation. In some instances the fellow bone of the leg or forearm is cut obliquely and shortened or a cross section is removed in order to reduce or eliminate the space between the ends of the fragments.

The site of the graft, usually the anteromedial surface of the tibia of the opposite leg, is exposed subperiosteally and the graft is excised with a motor saw. Before cutting the graft the holes are drilled for the screws. These

are slightly larger than the metal screws in order that the graft may be screwed tightly against the bone. Then, the graft is firmly fixed to one fragment with two or three metal screws and the other fragment is then placed in position and the graft also fixed to it. A series of small drill-holes are then made near the end of each fragment (multiple drilling) and

FIG 7

FIG 8

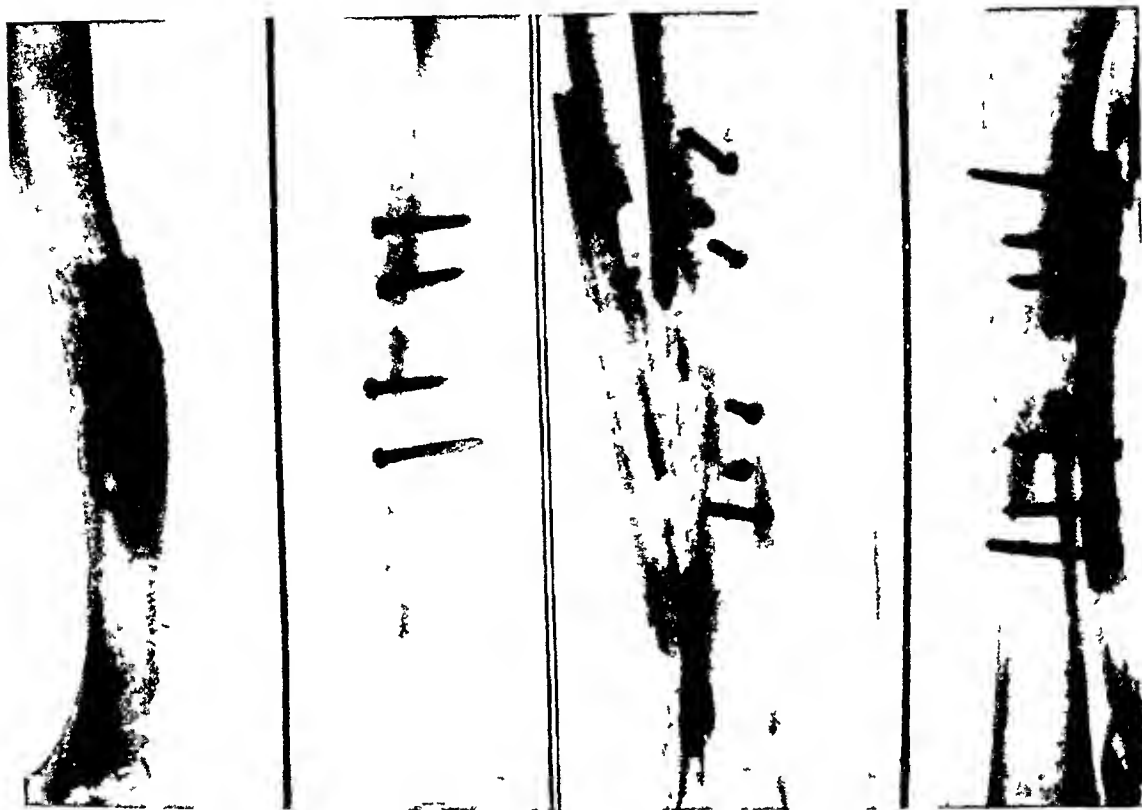


FIG 7—Same eight weeks after onlay graft, plus cancellous bone and splinter grafts and drilling and opening of the marrow canal. Had been immobilized in a "hanging cast." Union was firm.

FIG 8—Old nonunion of the tibia with loss of substance. The leg was shortened about one half inch by sliding the fibula up, and the fragments were fixed with an onlay graft and drilled, and the remaining defect filled with cancellous bone and bone splinters and chips. Immobilized in a plaster encasement for three months, until union was firm. In the meantime the patient fractured the other leg (Fig 3).

several small pieces of the cancellous bone from the proximal end of the tibia are scooped out with a large curette or gouge and are pressed down against the fracture line. Also, two or more small slivers of bone are cut from the margin of the defect from which the graft was taken and are placed across the fracture line on the side of the bone opposite the graft. If there is a space between the ends of the fragments, this is packed with cancellous bone and bone chips. Slivers of bone are then curled up from the side of the graft defect in the tibia and the wounds are closed and the extremity is immobilized in a plaster encasement (Figs 7, 8 and 10).

The onlay graft is then a bone plate of heavy cortical bone. In recent years I have sometimes reinforced the graft with an oblique screw, as used by Darrach and Murray in their bone-plating operations in order to increase the rigidity of the fixation (Fig 11). This operation has certain

FIG 10



FIG 9

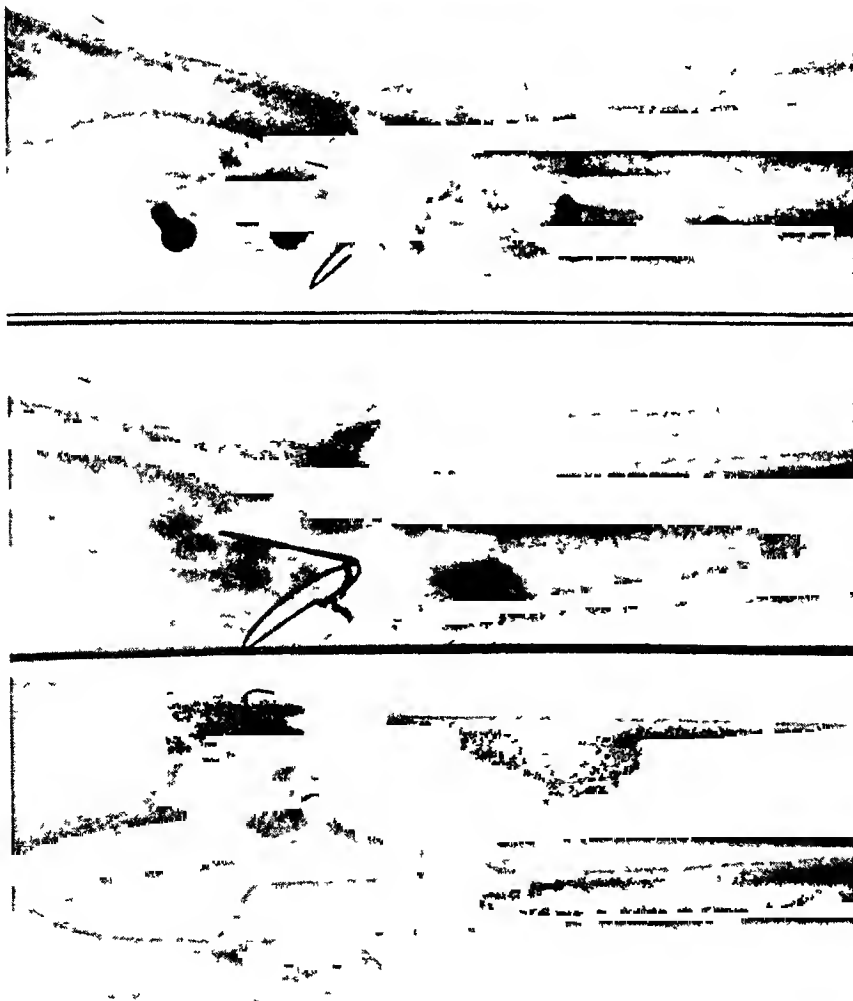


FIG 9.—Old nonunion after open reduction and wiring.
 FIG 10.—Same after onlay graft, multiple drilling and necessary bone to fill the dead space beneath the graft. The wires were not exposed. Immobilized in a plaster encasement for ten weeks. After union was firm a sinus developed on the mesial side over the wire. This and the screws were removed and there has been no further trouble.

disadvantages and limitations Due to the considerable amount of metal left in the wound it should not be used in infected or recently infected bone if some other type of graft offers a fair chance of success I have recently removed the screws from a Buchanan-type of graft done about three years ago This was an old infected compound comminuted fracture and the graft was laid in the medullary canal of the distal fragment because much of the cortex was lost Over two years later a low-grade infection developed around one of the stainless steel screws As it increases the thickness of the bone by the size of the graft it should not be used in subcutaneous areas, and is rarely used in the forearm It is preferably used on surfaces well covered by muscle Due to the fact that at least two screws should be placed in each fragment it is not suitable if one fragment is quite short as it may interfere with the movement of the joint

In spite of the objections mentioned above, I consider the onlay graft, as described above, as the standard operation for nonunion of long bones In my hands the inlay graft has not furnished very secure fixation and it has been reserved for subcutaneous areas, such as the malleoli and the distal third of the leg and forearm

During the past year, or longer, we have been experimenting with the massive onlay graft placed posterior to the tibia, without internal fixation The operation is attractive because of its simplicity It is suitable only in instances where the fragments are in satisfactory position and fixed by fibrous tissue, that is, cases where multiple drilling might result in union, but where a little extra stimulus to osteogenesis is desired An incision is made along the posteromesial border of the tibia and, with a sharp osteotome thin slivers of bone and the periosteum are elevated from the posterior surface of the bone at the line of the fracture and a short distance on either side This provides a flat bed of raw bone for the graft with periosteum and some bone over it Then, a relatively wide, short full-thickness graft is removed from the proximal third of the anteromesial surface of the same or the opposite tibia The fat is wiped from the endosteal surface and with this surface next to the tibia one end of the graft is driven upward and inward behind the tibia The lower end of the graft is then pushed in and driven home with a nail set Several holes are drilled across the fracture line and bits of cancellous bone are pressed in around the fracture line and the wound is closed (Figs 14, 15 and 17) We have called this the Phemister graft because it is similar to the method described by him a few years ago Phemister¹³ used it in all long bones and even in bones which were infected

We have also used multiple thin grafts of cortical bone placed across the fracture line around the bone (the barrel stave grafts of Steel), but where we have used these we have also used a bone plate for internal fixation (Figs 18 and 19) and have on one occasion used the thin cortical bone graft beneath a noncompressive plate as advocated by McBride¹⁴

The above operations all resulted in union in the cases in which they were used, and it is possible that the more formidable onlay graft fixed by metal screws has been used in cases in which a simpler procedure would have been successful. On the other hand, when operating for nonunion it is advisable to do a little more, rather than a little less, than will be necessary

to secure the desired result because the patient has already had an unusually long period of disability following his injury.

In nonunion of fractures of both bones of the forearm and other small bones and in fractures near the ends of long bones and of the olecranon, the intramedullary autogenous bone peg is the operation of choice, even though it is condemned by many surgeons. A round hole ($\frac{1}{4}$ of an inch for the radius or ulna) is drilled into the marrow canal of each fragment and a square peg of approximately the same diameter is cut from the tibia and driven tightly into one fragment and then forced by pressure into the other fragment. Then a small hole is drilled through each fragment (not through the peg) and a loop of stainless steel wire is

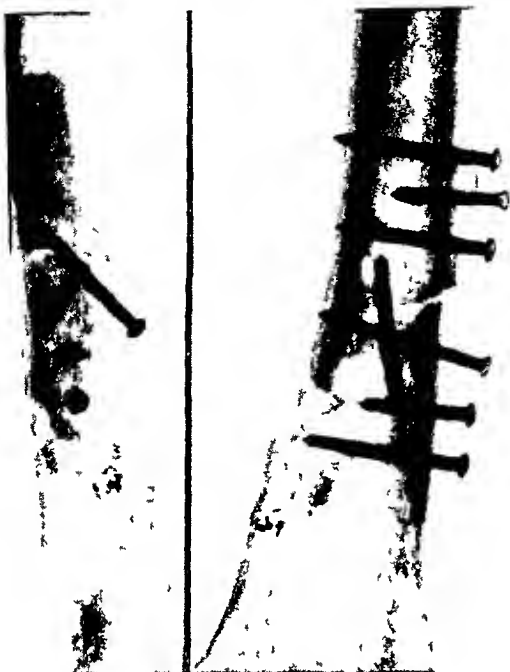


FIG. 11.—Nonunion of the femur treated by an onlay graft with multiple drilling and necessary bone and a long oblique screw at right angles to give rigid fixation. Immobilized in a plaster spica for three months.

twisted tightly to pull and hold the fragments together. The failure to use this wire is one cause of failure in this type of graft. Finally some shivers of bone and bits of cancellous bone are placed around the fracture-line (Figs 4 and 5).

I have not used the Albee wedge graft, but have used a massive graft with reduced square ends to fit in round holes to span relatively large defects. This is really a modified medullary peg. Likewise, I have had no experience with the method of Gill, who splits off a massive graft to include about half of the thickness of one fragment and slides it down to bridge the defect and fixes it to the ends of each fragment with metal screws.

Osteoperiosteal grafts, sliver grafts, bone chips and cancellous bone are useful mainly to fill defects and to stimulate osteogenesis at the site of nonunion which is bridged by some other type of graft or a metal plate. I believe that more experience will increase the use of Abbott's iliac grafts combined with bone plates.

After any of the above operations the wound is sprinkled with sulfonamide powder and closed without drainage. The suture line is sprinkled

FIG 12



FIG 13



FIG 12—Nonunion of forearm of nine months duration, with two previous operations. Treated by onlay grafts, with multiple drilling and accessory bone. Immobilized in a plaster encasement for ten weeks.

FIG 13—Old nonunion of the tibia after open reduction and wiring.

FIG 14



FIG 15



FIG 14—Same after Phemister splint graft, with multiple drilling and accessory bone. The wire was not exposed, but was cut during the drilling. Immobilized in a plaster encasement for ten weeks.

FIG 15—Old double fracture, with nonunion of both. Treated by long splint graft fixed by screw to middle and distal fragments. Both fractures were drilled and accessory bone was used. Immobilized in a plaster encasement for eight weeks, then active exercise.

with sulfonamide powder and the limb is immobilized in a plaster encasement applied over a thin dressing and very little padding. This encasement

is not intended to allow walking, and it is left on until sufficient time has elapsed for the development of fairly firm union (eight to twelve weeks). The wound is not inspected nor are the skin sutures removed until the encasement is removed. Early change of plaster or the cutting of a window in the plaster may result in angulation of the fragments or even fracture of the graft or loss of position and weight-bearing may disturb immobilization. The patient usually leaves the hospital a few days or a week after the operation and when he returns the encasement and sutures are removed, roentgenograms are taken and the stability is tested and, if necessary, a new encasement is applied for four weeks or more, but this is rarely necessary.

CONCLUSIONS

1 With the added insurance against infection provided by the local use of sulfonamide powder in the wounds, operations for the cor-

rection of delayed and nonunion of fractures should be performed earlier than in the past.

2 The surgeon should choose an operation which he is able to perform satisfactorily and which can be expected to result in union of the fragments in good position.

3 The simpler procedures are less apt to be followed by postoperative complications than are the more difficult operations, but they will not solve the more difficult problems.

4 A relatively simple operation, if undertaken early, may save the patient time, avoid a difficult late operation, and result in a better limb.

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FIG 17

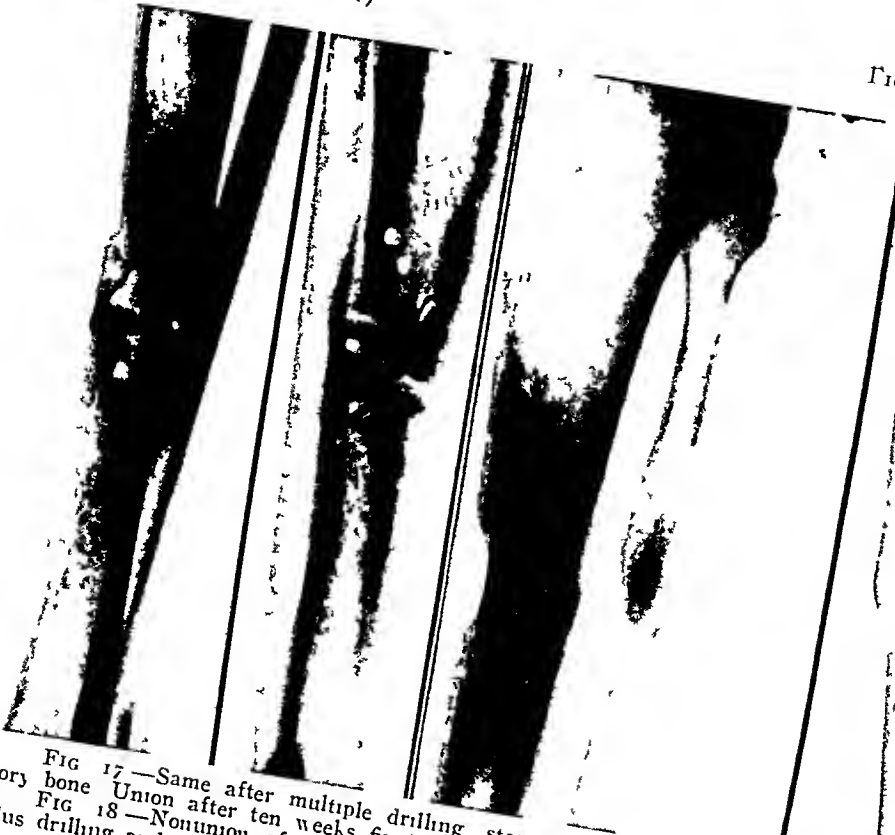


FIG 18



FIG 17—Same after multiple drilling step cut operation, wire fixation, splint graft and accessory bone Union after ten weeks fixation in a plaster encasement
FIG 18—Nonunion of tibia fixed by a bone plate and multiple barrel stave grafts of Steel, plus drilling and accessory bone to secure union



FIG 19—Old subtrochanteric fracture which had had three previous operations Fixed by Neufeld nail and multiple barrel stave grafts, plus drilling and accessory bone used to secure union Immobilized for four weeks in plaster boots fixed to a crossbar to maintain abduction

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THYROCARDIAC DISEASE¹

A REVIEW OF 614 CASES

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IN THE LAST TWENTY-FIVE YEARS the advances in the surgical treatment of the thyrocardiac and the results of surgery in the patient with hyperthyroidism limited cardiac reserve have been striking and gratifying. These advances fall naturally into five definite periods.

In the first period, approximately twenty-five years ago, many cases of hyperthyroidism with cardiac failure were not even diagnosed. Many times the physician failed to appreciate that the cardiac failure resulted from the associated hyperthyroidism. Most patients with a diagnosis of thyroid disease and associated cardiac failure were rejected as hopelessly inoperable, because the mortality was almost prohibitive.

The second period started a little over twenty years ago when Hamilton,¹ who was then associated with the Lahey Clinic, published his first paper on heart failure and hyperthyroidism. In 1924, Hamilton and one of us (F H L)² described the diagnostic difficulties and surgical treatment of these patients and applied to them the term thyrocardiac. In this pioneer era in the management of patients with cardiac decompensation associated with hyperthyroidism, it was demonstrated that these patients could endure subtotal thyroidectomy with a reasonable mortality and that subsequently an extraordinary degree of activity and cardiac capacity were restored and retained.

The third period, in which iodine was popularized by Dr H S Plummer, of the Mayo Clinic, was a most important one in the surgical treatment of hyperthyroidism, since it contributed so materially to reduction of operative mortality.

The fourth period, which may be described as the total ablation period, was advocated by Blumgart, Levine and Berlin.³ This method has been discarded here and largely elsewhere. The reasons are obvious after a careful study of Figure 1, which shows the relation of the circulation rate to cardiac damage and metabolic rate, and the anticipated results in patients with decompensation without the promoting and removable factor of hyperthyroidism.

The fifth, and present, period is characterized by a much better understanding of what causes decompensation in a patient with hyperthyroidism (Fig 1) why the patient is so dramatically benefited by subtotal thyroidectomy, and why the benefits of subtotal and total thyroidectomy in a patient

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with decompensation but without hyperthyroidism are so transitory. This period is characterized, further, by an improved understanding of oxygen needs, preoperative preparation, anesthesia selection, postoperative care, and less importantly, vitamins. In spite of these advances the mortality continues to be high and, we believe, could be lowered.

In the sixth, and future period, we hope that the diagnosis will be made in the early stages of decompensation and that surgery will be undertaken before decompensation and auricular fibrillation have existed over a long period of time. In this anticipated period, we hope the internist will realize that

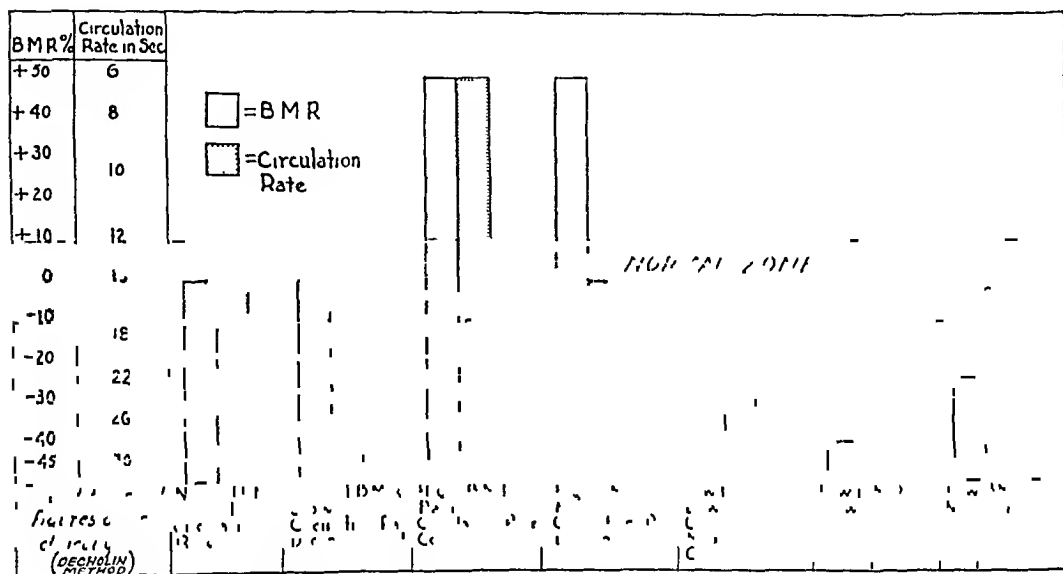


FIG 1—Relationship of circulation rate to metabolic rate in various types of thyroid disease and hypometabolism

cardiac decompensation is found much more frequently in patients with toxic adenoma than in patients with primary hyperthyroidism. We hope the internist will appreciate that while young persons with toxic adenomata, and some limitation of cardiac reserve, frequently fail to show cardiac decompensation, persons past 50 years of age, with the effects of age effort and disease upon the heart, tend much more frequently to show decompensation. Such is the association of cardiac decompensation with toxic adenoma that in this future era the removal of mildly toxic adenomatous goiters in patients over 50 years of age might reasonably be suggested as a prophylaxis against later cardiac decompensation. We believe that in the presence of auricular fibrillation with hyperthyroidism, immediate surgery is justifiable, in spite of the fact that auricular fibrillation may produce few symptoms. When one realizes that auricular fibrillation and hyperthyroidism are the two most important factors in producing decompensation that subtotal thyroidectomy will eliminate hyperthyroidism almost at once and will restore normal rhythm in 72 per cent of cases, the prophylactic benefit of prompt surgery with the onset of auricular fibrillation is evident.

WHAT IS A THYROCARDIAC?^{1,7}

The term thyrocardiac has a limited meaning and does not include patients with hyperthyroidism and simple heart disease. Even though the operative risk may be above average, such a patient is not labelled as a thyrocardiac. In our early reports² we realized the necessity of defining the term thyrocardiac, first, to avoid misunderstanding as to the type of case, and, secondly, to include only those cases in which the heart complications seemed definitely attributable to the overactive thyroid.

In the great majority of thyrotoxic patients, auricular fibrillation is a manifestation of hyperthyroidism. Congestive heart failure results from excessive thyroid drive on the heart in most instances with auricular fibrillation but in some instances with regular heart rhythm. The most conclusive reasons for this deduction are that following subtotal thyroidectomy auricular fibrillation usually clears spontaneously and that recurrent congestive heart failure following subtotal thyroidectomy is exceedingly rare without recurrence of hyperthyroidism or severe heart disease unrelated to hyperthyroidism. Thus, a thyrocardiac has a condition precipitated by hyperthyroidism and relieved by cure of the hyperthyroidism.

We wish to emphasize that a true thyrocardiac has clinical hyperthyroidism. This does not mean only an elevated metabolic rate, which may occur in congestive heart failure without hyperthyroidism, nor does it mean a large nontoxic goiter, auricular fibrillation or congestive heart failure resulting from other heart disease without clinical hyperthyroidism. A true thyrocardiac has well-recognized hyperthyroidism, as may be deduced from the history and from the general physical findings. A true thyrocardiac, with few exceptions, has an elevated basal metabolic rate.

A cardiac patient, even one with congestive heart failure, who is operated upon for nontoxic or questionably toxic goiter, apparently may be benefited for a limited time. Generally speaking, if the evidence of hyperthyroidism in a cardiac patient is minimal or questionable, so then is his likelihood of permanent help and sustained restoration of compensation by subtotal thyroidectomy. The enforced rest, the preoperative cardiac care, and the careful postoperative regimen are largely responsible for the improvement following removal of a nontoxic goiter unless the combination of heart disease and a compressed trachea is present. In addition, the frequent production of postoperative thyroid deficiency or myxedema, as was demonstrated in total ablation, lessens the load on the heart only temporarily. Thus, we have not seen permanent relief from subtotal thyroidectomy in patients with goiter and heart disease without hyperthyroidism and do not recognize such an entity as cardiotoxic goiter, as described by Schmidt and Heitzler.⁴

Heart failure in hyperthyroidism is a manifestation of inability of this organ to meet the abnormal demands of an increased metabolism. Heart failure without hyperthyroidism is a manifestation of inability of this organ to meet the usual demands of a normal rate of metabolism (Fig. 1). Thus, the cessation of the abnormal demands of hypermetabolism relieves the unusual

strain on the heart, so that when normal conditions return, the heart is capable of carrying on without difficulty

In brief summarization

1 No conclusive evidence exists that hyperthyroidism damages the heart although it may produce physiologic exhaustion

2 Auricular fibrillation in hyperthyroidism is not in itself evidence of structural damage

3 Gross cardiac hypertrophy from hyperthyroidism rarely occurs without coincident cardiovascular disease

4 The large heart shadow in some thyrocardiac patients is the result of dilatation from congestive heart failure and return to normal size may be expected in the majority of patients⁵

TREATMENT

Preoperative—The preoperative treatment of the thyrocardiac patient involves two principles

1 Reduction of the level of metabolism, and thus the work of the heart by (a) rest in bed, (b) administration of Lugol's solution, and (c) sedation as needed

2 Increase in the efficiency of the heart by (a) digitalization if auricular fibrillation is present, (b) removal of the embarrassment of circulation caused by edema, ascites or pleural effusion through the use of salt restriction but not the restriction of fluid, by the use of diuretics, or by paracentesis, (c) venesection and oxygen in rare cases, and (d) an abundant supply of fuel in the form of various carbohydrates, and an adequate nutritional diet including the necessary vitamin factors

Thyrocardiac patients also require longer preoperative preparation than the ordinary patient with hyperthyroidism. Surgery should not be undertaken too soon, even though some patients may die unoperated. Generally speaking, at least two to three weeks of preoperative treatment are advisable.

Operative—Because the condition of the thyrocardiac is frequently so desperate and the results of surgery are so dramatic, we assume that no doubt exists, particularly in the minds of those familiar with these cases, that subtotal thyroidectomy is the best and practically the only treatment. The procedure must be a radical subtotal thyroidectomy to avoid a persisting or recurring hyperthyroidism. Unlike the patient with hyperthyroidism only, often the patient has failed to retain compensation in spite of all attempts to limit the hyperthyroidism, short of surgery, and to increase cardiac capacity. Thyroidectomy in the dangerously ill thyrocardiac has a high mortality and consequently must be performed with the aim of preventing even minimal complications.

The patient must be protected against hemorrhage. During the operation this complication interferes with technical accuracy, prolongs the operation, produces shock and promotes anoxemia by depleting the oxygen-bearing blood cells. Postoperatively, this complication involves the hazards of a second operative procedure soon after the first and during a period of reaction.

Tetany has not occurred in any patient in this series, and obviously would be a most undesirable postoperative complication

As we have already said, perhaps one of the most undesirable complications is the inadequate removal of thyroid tissue, resulting in persistent hyperthyroidism or recurrent hyperthyroidism with the danger of recurrence, decompensation and secondary operation

To avoid operative and postoperative complications, the surgeon should obtain adequate exposure without reference to the length of the incision. He should keep in mind the ease with which the operation can be performed, and the certainty with which complication can be avoided, and to this purpose, the incision in the skin should be wide, the muscles should be cut, and the lobes should be completely mobilized from their beds. Since a radical removal as

TABLE I
POSTOPERATIVE MORTALITY

Year Group	Number Operated	Percentage Mortality
1922-1931 inclusive	303	4.3
1932-1936 inclusive	170	7.0 [*]
1937-1941	141	11.3
1922-1941	614	6.6

*Erroneously reported as 4.7 per cent of 136 operated cases⁶, actually 7 per cent of 140 operated cases

possible is desirable, the superior and inferior thyroid arteries on both sides should be tied as a preliminary measure. With wide exposure of the thyroid and a dry field, with accurate demonstration of the nerves, parathyroid glands and the entire thyroid gland, total thyroidectomy can be undertaken expeditiously and with almost complete avoidance of technical difficulties

While a one-stage subtotal thyroidectomy is desirable in thyrocardiac patients for quick and complete removal of the cause of the decompensation, occasionally because the patient is dangerously ill, a compromise must be made. The cooperative judgment of a surgeon, anesthetist and internist experienced in thyroid disease are of the utmost value. Certain patients will require one-stage, two-stage and occasionally three-stage procedures in order to maintain the mortality rate within limits which are even now undesirably high (Tables I, II and III)

Anesthesia—An operation upon a thyrocardiac must involve as few operative and postoperative anesthetic complications as possible. The oxygen requirements of the patient with hyperthyroidism during anesthesia are well above those of normal persons, and the maintenance of an adequate supply of oxygen is important. In reviewing our thyroid experiences before employing endotracheal anesthesia to insure unobstructed airways, we were impressed in the thyrocardiac particularly with the fact that prolonged laryngeal spasm or the accumulation of mucus during the recovery period resulted in prolonged and dangerous anoxemia and may have played a rôle in resulting fatalities. Endotracheal anesthesia, as we frequently have observed, is one of the most important contributions to thyroid surgery especially in the thyrocardiac.

Another important contribution is the aspiration of all mucus from the

TABLE II
NATURE OF POSTOPERATIVE DEATHS

After subtotal thyroidectomy	
'Storm	
Age 34 41	2
After pole ligation only	
'Storm	
Age 56 67	2
After elevation of skin flap only, died on table	
Previous cerebral embolus	
Age 50	1
Gallop rhythm history of coronary attack diabetic	
Age 70	1
After hemithyroidectomy preceded by pole ligation four weeks previously	
'Storm	
Age 69	1
After second hemithyroidectomy preceded by two pole ligations and hemithyroidectomy four to six weeks previously	
Storm	
Age 78	1
After hemithyroidectomy	
Pulmonary embolism	
Age 58	1
Cerebral and peripheral emboli	
Age 62	1
Probable cerebral embolus	
Age 64	1
'Storm	
Age 40 57 63 63 70	5
Total	16

TABLE III
TYPE OF OPERATION AND POSTOPERATIVE DEATHS
Operation*

Number	Type	Percentage	Deaths
56	One-stage	40	3
63	Two-stage	44	8
20	Three-stage	15	4
2	Four-stage	1	1

*Type of operation planned and carried out unless death occurred before all procedures were performed

trachea just before removal of the intratracheal catheter, thus, often preventing tracheal obstruction and resulting anoxemia which occurs during recovery from anesthesia before the patient regains the ability to eject spontaneously the accumulated mucus in his bronchi

No factor is more important in operative mortality in the thyrocardiac than the selection of the proper anesthetic agent. In the period before the present one, we enthusiastically advocated the use of cyclopropane particularly because of the high percentage of oxygen in a cyclopropane mixture. However, we have had three operative deaths in thyrocardiacs from probable ventricular fibrillation promoted by cyclopropane. One of these deaths was literally heard in the stethoscope while the anesthetist was taking the blood pressure, that is, sudden and complete cessation of all pulse sounds. We now employ cyclopropane in thyroid patients and particularly thyrocardiacs only as an induction agent and then only in mixtures not exceeding ten per cent Ethylene, without the tendency to produce cardiac irregularities is a satisfac-

tory induction agent for the thyrocardiac. As a result of these experiences with ethylene and cyclopropane, and following the published⁷ laboratory data on the effect of cyclopropane upon the epinephrine sensitized heart, cyclopropane has now been largely abandoned in favor of ethylene supplemented with ether. We now realize that in giving cyclopropane to a thyrocardiac we were superimposing another cardiac irritant upon a heart muscle already suffering from a cardiac irritant—thyroxin.

The physician is apt to think that the thyrocardiac, often having had associated ascites, edema, orthopnea and cardiac irregularities, is too ill for inhalation anesthesia. Because of this and because the patient is awake and is not inhaling an anesthetic agent he easily can be misled into believing that local anesthesia is safer. However with a proper inhalation anesthetic and an intratracheal catheter in place the patient may often be breathing a richer mixture of oxygen than when under local anesthesia.

The two most advantageous features of an inhalation anesthetic are (1) the employment of an intratracheal tube or airway thus supplying an adequate and constant supply of oxygen, and (2) the production of definite relaxation with a good supply of oxygen and as little irritation to the heart muscle as possible.

For the thyroid patient, and specifically for the thyrocardiac, local anesthesia has not only no advantages but many disadvantages. The disadvantage for the patient is the creation of undesirable emotional and psychic states, and the disadvantages for the surgeon are that it fails to permit adequate exposure, a dry field and a clean-cut anatomic dissection. In addition, a longer period of time is necessary to perform the operation.

Avertin, while attractive from both the patient's and surgeon's point of view in permitting transportation of the patient to and from the operating room while asleep, is an undesirable anesthetic agent for the patient with hyperthyroidism and particularly for the thyrocardiac. It is followed by a long period of postoperative depression, with accumulation of bronchial secretion, and sometimes with the undesirable complication of an inadequate supply of oxygen.

After a number of years of combined effort by the surgeon, anesthetist and cardiologist, we have concluded that ether is the safest and most satisfactory anesthetic agent for the thyrocardiac. This is a radical change of viewpoint from some of our previously expressed opinions, and certain qualifications concerning the use of ether are necessary. We are strongly opposed to ether as an induction agent, since it promotes psychic stimulation, agitation and struggling, and requires a long time. The safest anesthetic procedure for the thyrocardiac is to give 15 grains of pentobarbital sodium the night before operation and $\frac{1}{6}$ gram of morphine and 1/150 grain of scopolamine one and one-half hours before operation, followed by 15 grains of pentobarbital sodium one hour before operation and then induce anesthesia with ethylene and continue with ether.

Postoperative—All patients with hyperthyroidism with or without car-

diac damage, are placed in oxygen tents postoperatively to facilitate breathing, and particularly in thyrocardiacs to lighten the load upon the heart. Saklad⁸ called attention recently to the necessity of tents that do not leak, and the frequent testing of content to be certain that the oxygen percentage is being maintained at the desired level. As he pointed out, because of lack of supervision many patients undoubtedly never receive an adequate percentage-mixture of oxygen.

Thyrocardiacs, as well as all other patients operated upon for hyperthyroidism, receive an intravenous glucose solution postoperatively. One must be careful, however, lest cardiac embarrassment results from too enthusiastic employment of this useful measure. Intravenous glucose in five

TABLE IV
PERCENTAGE OF AURICULAR FIBRILLATION PERSISTING TO
DATE IN OPERATED PATIENTS

Year Group	Percentage	
1922-1931 inclusive	27	
1932-1936 inclusive	28	
1937-1941 inclusive	26	
	Persistent	Percentage
Normal	Auricular	Auricular
Rhythm	Fibrillation	Fibrillation
222	84	27

per cent solution may be given in quantities not exceeding 2 000 cc. in 24 hours. With the increase in metabolism following operation the body can easily handle this quantity in addition to that taken by mouth. The cardiac burden will not be increased if the solution is given slowly, at least two hours being taken for the introduction of each liter of fluid.

Iodine is administered in intravenous solution at the rate of 30 minims in 24 hours. Morphine in liberal amounts to reduce restlessness is desirable, but care must be taken not to overdo the use of this valuable drug, thus completely suppressing the cough reflex and inducing the extremely dangerous postoperative complication of pneumonia.

For two or three days postoperatively the patient accumulates a good deal of mucus as a result of secondary tracheitis, and is in constant danger of partial or complete unilateral atelectasis. The mucus should be aspirated from the trachea with a rubber catheter when atelectasis has not taken place and bronchoscopy should be undertaken promptly, under local anesthesia, when partial or complete unilateral atelectasis has occurred. We have seen dramatic results follow suction bronchoscopy in thyrocardiacs with atelectasis following the removal of mucus from the bronchi and aeration of the atelectatic area.

Preoperative and Postoperative Quinidine Therapy—Quinidine should not be employed in thyrocardiacs until after the completion of all operative procedures. If it is used preoperatively to stop auricular fibrillation the irregularity almost certainly will return postoperatively.

While the majority of patients with auricular fibrillation have a return of normal cardiac rhythm within the first few months after operation, it can be

THYROCARDIAC DISEASE

restored more quickly by the use of this drug if given a week or so after the final operative procedure. We have not employed quinidine sulfate as much during the last five years as formerly, yet the percentage of persistent auricular fibrillation has remained fairly constant (Table IV). This would suggest that while quinidine postoperatively promptly restores normal rhythm, in most instances normal rhythm would have occurred spontaneously later.

On the basis of this experience, the value of quinidine sulfate for the thyrocardiac can be questioned. Since the drug is toxic, and must be given with caution, we doubt whether its use is as advisable as we formerly believed. The fear of embolus following its use is its chief drawback, but, in our experience, this has occurred but once.

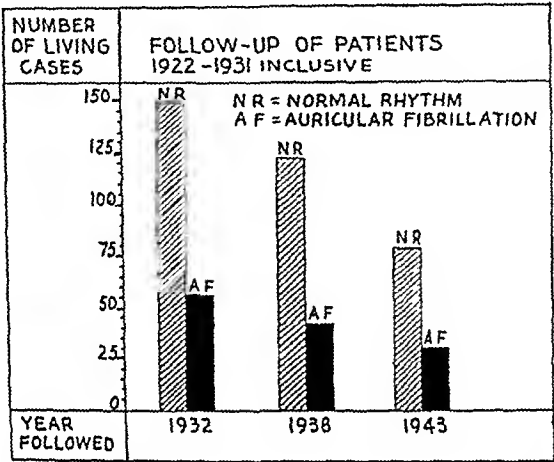


Fig. 2.—Ratio of persistent auricular fibrillation to normal rhythm in surviving patients operated upon between 1922 and 1931. Persistent auricular fibrillation does not increase death rate.

In spite of apparent subsequent embolic deaths in these cases, auricular fibrillation is probably no greater hazard than normal rhythm as far as life expectancy is concerned since death has occurred as frequently in the group of patients with normal rhythm as in those with auricular fibrillation (Fig. 2).

FOLLOW-UP STUDIES

Another follow-up of all thyrocardiacs recently was completed (Table V). This study was chiefly by questionnaire, many of which were completed by the patient's physician. Evaluation of the present results was established as follows:

- Grade 1 Patients able to carry on normal activities commensurate with individual age, with no myxedema, regular heart rhythm and no recurrence of hyperthyroidism.
- Grade 2 Patients still having auricular fibrillation or postoperative myxedema requiring thyroid, or having had a recurrence of hyperthyroidism controlled by iodine, who carry on normal activities.
- Grade 3 Patients incapacitated by any complication attributable to their thyrocardiac condition such as hemiplegia from embolus, incapacitating recurrence of hyperthyroidism, or congestive heart failure without hyperthyroidism.

TABLE V
PRESENT STATUS OF 611 OPERATED THYROCARDIACS¹
1922-1941 Inclusive

Year Group	Percentage Alive	Percentage Dead
1922-1931 inclusive	35	32
1932-1936 inclusive	54	24
1937-1941 inclusive	75	18
Known alive		306
Grade 1 201		
Grade 2 100		
Grade 3 5		
Known dead		165
Untraced		143
Incidence of postoperative myxedema		2.9%
Incidence of diabetes		3.6%
*At operation 60 per cent over 50 years of age		

We realize that patients may not always know whether the pulse is regular or irregular. If auricular fibrillation was shown by the record to have existed a year or more after operation, and the patient reported irregularity the condition was assumed to continue even when the rhythm was normal on last examination. The patient with probable auricular fibrillation was graded 2. Because of the improbability of a recurrence of auricular fibrillation without recurrence of hyperthyroidism, these patients were asked to return for reexamination, however, only a few patients made such a report. Thus, in reporting the presence of auricular fibrillation, we have erred on the side of a greater number having this irregularity than not having it.

TABLE VI
THYROCARDIAC CASES
1937-1941 Inclusive

Total number seen	147
Operated	141
Postoperative deaths	16
Died no operation	4
Refused operation	2
Preoperative cardiac status in operated patients	
Congestive heart failure with regular rhythm	10
Congestive heart failure with auricular fibrillation	56
Established auricular fibrillation without congestive heart failure	75
Total	141

A new group of thyrocardiacs, those patients operated upon from 1937 to 1941 inclusive, is reported (Table VI). In this group of patients followed from one to five years, the results are essentially the same as in the other groups followed for the same length of time.

SUMMARY

The name thyrocardiac, applied by one of us (F. H. L.²) to this condition in 1924, called attention to this interesting group of patients in whom early diagnosis and early subtotal thyroidectomy can accomplish such gratifying restoration of cardiac capacity and physical activity.

The present is the fifth period, so to speak, in the treatment of this condition. A sixth period is hoped for, in which earlier diagnosis and operation,

and even prophylactic subtotal thyroidectomy for early toxic adenomata and early auricular fibrillation would give even better results

The necessity in speaking of a thyrocardiac as one having indisputable hyperthyroidism is stressed. The reason the true thyrocardiac permanently regains cardiac compensation after subtotal thyroidectomy and the false thyrocardiac does not, is discussed under the heading "What Is a Thyrocardiac?"

The preoperative and operative management is discussed, as well as postoperative care and preoperative and postoperative employment of quimidine

The results of our experience with various types of anesthesia are discussed, and a conclusion reached as to the best combination of narcotics and anesthetic agents for the thyrocardiac

The end-results in 614 cases, from 1923 to 1933, and from 1933 to 1943, are presented

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DISCUSSION—DR. ROBERT S. DINSMORE (Cleveland). Doctor Lahey always presents material which is of prime clinical importance. The question of auricular fibrillation is extremely important in this group of cases as a whole, and I am sure that the incidence is much higher than is generally supposed.

In an analysis of 1000 consecutive patients with hyperthyroidism in our series, Ernstene found that 20.7 per cent had auricular fibrillation in one of three forms. It had occurred, first, as a paroxysm of fibrillation preoperatively, secondly, in the continuous form, and, thirdly, postoperatively, without evidence of congestive heart failure.

These figures vary slightly from Doctor Lahey's because if one takes these cases as a whole it is found that in the 20 per cent, about half of them have either an associated arteriosclerosis, a hypertensive disease, or an organic heart lesion.

In spite of bed rest, Lugol's, digitalis, and sedatives, we find nine per cent of these patients fibrillate preoperatively, and 11 per cent postoperatively. I have felt that this postoperative incidence was too high, and if there were some criteria whereby we could increase the number of patients who were digitalized before the operation, this postoperative incidence could be lowered. The present criteria for the cardiologist

in administering digitalis are First that the patient have auricular fibrillation, or second, evidence of congestive heart failure In our cases, four per cent had congestive heart failure, nine per cent fibrillated before the operation, so at most 13 per cent were digitalized preoperatively

The reason I have felt so strongly about this is because I saw a large series of cases during 1921-22 on Doctor Crile's service at Lakeside Hospital, in which the bane of our existence was the incidence of postoperative auricular fibrillation and the casualties that went with it This was before the days of Lugol's solution and Doctor Plummer's advice about that, so we started a large series of cases in which we routinely digitalized, and we were amazed to find a very marked drop in the incidence of postoperative auricular fibrillation

Some believe a postoperative auricular fibrillation is not of much significance, but I think, as Doctor Lahey has emphasized, that it is a danger signal It is not only a danger signal from the two points he has mentioned—namely, the possibility of congestive failure or the possibility of emboli—but also I have seen the onset of a postoperative auricular fibrillation be the initial sign in a long and stormy convalescence, particularly in the elderly patient who develops this arrhythmia, edema and bronchitis, and occasionally bronchopneumonia In spite of chemotherapy we still have occasional deaths in this group

On the question of angina with regard to the thyroid I thoroughly agree with Doctor Lahey, with regard to total ablation and in our hands it has been absolutely ineffectual I have discarded the procedure as far as I can and I have no confidence whatsoever in the operation I have thought the best result I had was in a man who had had anginal symptoms I removed the thyroid He was very much elated about the result because instead of being able to walk one block he was able to walk two blocks without pain However, a short time after that he died with a typical coronary episode That is about our experience with these cases I am quite sure that Colonel Claude Beck has made a more rational suggestion in handling anginal cases than anything the thyroid surgeon has to offer

I also want to give a note of warning about the use of quinidine We use it a little differently than Doctor Lahey does We have chosen the seventh postoperative day for its use in the patient who has had continuous fibrillation We do this because it is about the end of the hospital stay, and we like to give them the quinidine while they are in the hospital in bed We start them on three grains four times a day, or 0.2 Gm, and continue it until a normal rhythm is restored, and something over half of these cases have reverted to a normal rhythm

I want again to warn that the housemen, or whoever is responsible for the administration of the quinidine, know the four contraindications for its use First of all, be sure that this patient has had no history of previous embolic accident, that the heart is not enlarged, that he has no associated organic heart disease, and, above all, that he has no idiosyncrasies for the drug

I have had a little different experience with avertin than has Doctor Lahey I personally have used it over a ten-year period in thyroid work I agree with him that it has a full anesthetic effect, and that it is a bad anesthetic particularly in elderly patients, since they do get a marked cerebral depression, for this reason I do not like it for these cases I have used it in conjunction with local anesthesia, however, and the ordinary case receives from 65 to 70 mg per kilo of body weight These patients are really drowsy, but they can be aroused at any time, and in conjunction with local anesthesia it has been entirely satisfactory in my hands It is an ideal anesthetic for the very young child, three, four or five years of age, with a severe exophthalmic goiter

Again I want to repeat, as Doctor Lahey has stated, that it is a great satisfaction and gratification to have one of these desperately ill patients with a congestive heart failure, following a slow, unhurried preparation, have no postoperative cardiac complications following thyroidectomy

DR FRANK H LAHEY (Boston, closing) To avoid confusion in the results of treatment, it is important that we all have the same understanding of the term "thyrocardiac"

A patient with hyperthyroidism and a compensated cardiac lesion is not a thyrocardiac

A patient without hyperthyroidism and with a large nontoxic goiter and a cardiac condition is not a thyrocardiac. A true thyrocardiac is a patient with hyperthyroidism and resulting cardiac failure. That does not mean even that a patient with an increased basal metabolism and an enlarged thyroid gland who has cardiac decompensation is a thyrocardiac.

Unfortunately, we still have to use our senses in clinical and laboratory diagnosis. A patient, particularly with the hypertensive type of cardiac failure, can have an increase in metabolism up to +40 per cent. To establish the diagnosis that a patient is a thyrocardiac, one needs clinical evidence of hyperthyroidism, an increase in basal metabolism as a result of hyperthyroidism, and cardiac failure as a result of the circulation rate caused by the hyperthyroidism.

There are a few other things which I should like to mention. Is there such a condition as a true thyroid heart? There has never been any convincing evidence, microscopic or otherwise, that hyperthyroidism by its direct effect upon heart muscle produces damage. Auricular fibrillation does produce a rhythm which in the overburdened heart of hyperthyroidism tends to produce failure, but concerning that I can only say that auricular fibrillation frequently is associated with hyperthyroidism and is not, in itself, necessarily evidence of heart damage from thyroid intoxication.

We repeatedly have stressed the importance of keeping this group of cases in mind to avoid overlooking them, particularly because the urgency of the decompensation in the apathetic type of hyperthyroidism so often associated in the elderly with decompensation and hyperthyroidism, confuses the picture and makes the diagnosis difficult. Diagnosis is important, as evidenced by our end-result figures, because there is an excellent opportunity to restore these patients dramatically to long-continued and useful activity.

SKIN REMOVAL IN RADICAL BREAST AMPUTATION¹

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MOST of the debatable questions concerning cancer of the breast have been answered by carefully prepared statistics of postoperative results. Nearly fifty years have elapsed since Halsted published his first paper, in 1894, based on the first fifty cases operated by his method from which all modern operative procedures spring. Many have contributed to it since then. It is not, therefore, the object of this paper to reemphasize facts generally accepted.

Lewis and Rienhoff's paper, published in the *ANNALS OF SURGERY*, in March, 1932, covered in detail the statistical data of the results of the operative treatment of cancer of the breast at the Johns Hopkins Hospital from 1889 to 1931. This paper was based on 950 cases, 750 of which were operated upon by 38 different surgeons. Haagensen and Stout, in the *ANNALS OF SURGERY* for December, 1942, have added an excellent statistical study of 1040 cases observed from 1915 to 1934, 640 of whom had radical mastectomies. These operations were performed by 36 different surgeons at the Columbia Medical Center in New York City. In these two papers particularly, those interested will find many important problems discussed and answered by statistical data.

There are, however, still a few questions apparently unsettled—one of these, the oldest of all in radical breast surgery, is the question of skin removal. This question is important since it inevitably leads to the other problems still debatable—local recurrences and the necessity of skin grafting. In a paper read before this Association last year, William C. White, of New York, reported 238 cases operated upon by him and other members of the Staff of the Roosevelt Hospital. He expressed a preference for the Handley technic, and gave the impression that wide skin removal was secondary in importance to fascial removal. In this group, however, there were 22.6 per cent of local skin recurrences, while in the larger group studies by Lewis and Rienhoff there were 19.2 per cent local recurrences, and in the group studied by Haagensen and Stout, the statement is made that "the incidence of local recurrence in the operative field continues to be distressingly high—22.8 per cent of those surviving five years."

A special interest in this subject, now for the past 35 years in the first eight of which I had the opportunity of assisting my father, had led to certain firm convictions on these still debatable questions which are

First, that wide skin removal is important since, in our opinion, it must be the chief reason for local recurrences when insufficient skin is removed.

Second, that by combining wide skin and fascial removal such recurrences can all but be eliminated.

¹ Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

SKIN REMOVAL IN BREAST CANCER

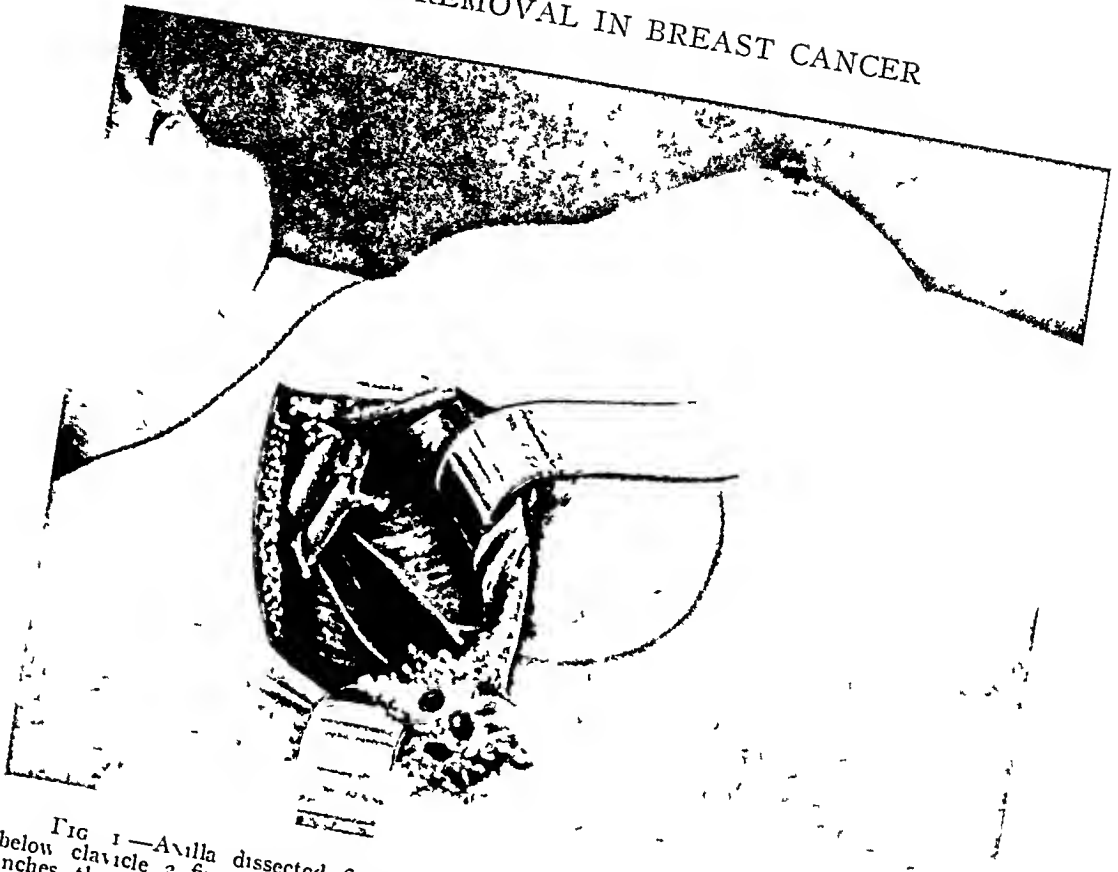


FIG 1—Axilla dissected first. Straight incision on chest wall beginning 1 inch below clavicle 2 fingers' breadth from edge of shoulder extending downward 4 or 5 inches through skin and subcutaneous fat—Pectoral portion of pectoralis major and tendon of pectoralis minor divided at their insertions. Axillary node tearing from fascia dissected from above downward. Vessels ligated at source of origin. Subscapular nerve on posterior wall and long thoracic (external respiratory nerve) on inner wall preserved.

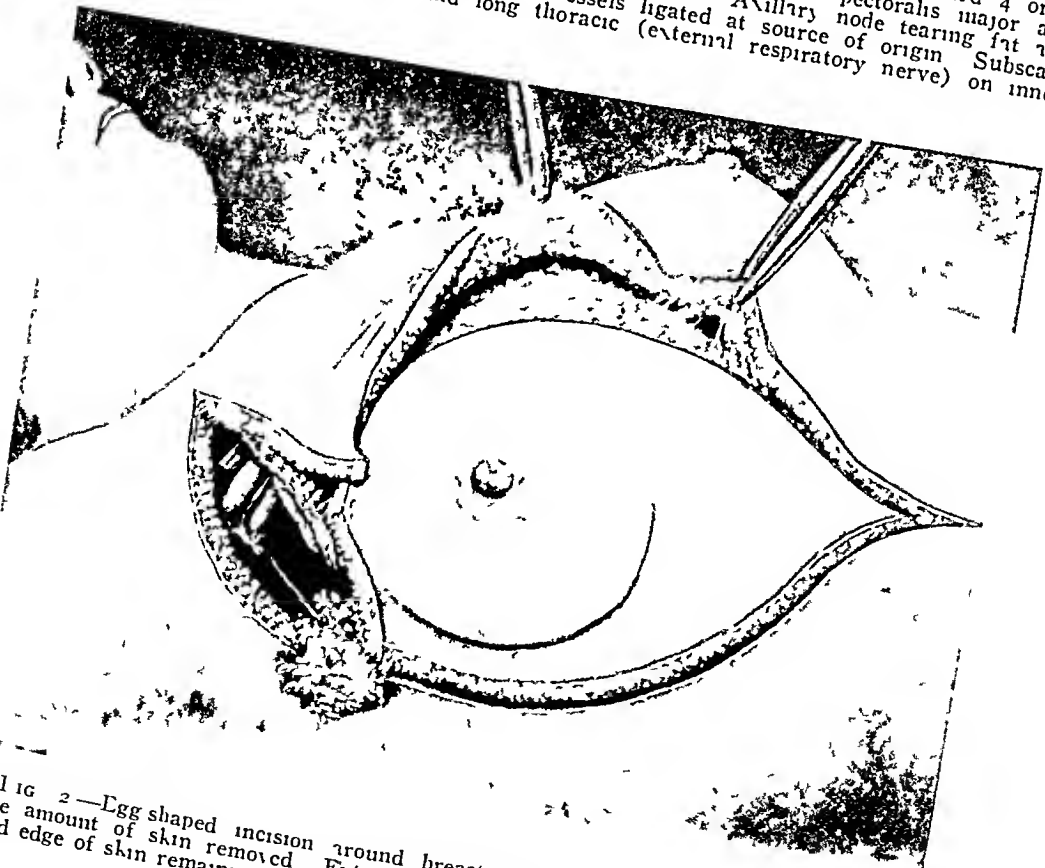


FIG 2—Egg shaped incision around breast and well down on to upper rectus. Large amount of skin removed. Extensive undermining of skin begun. At no point should edge of skin remaining have been closer than 2 inches to edge of growth.

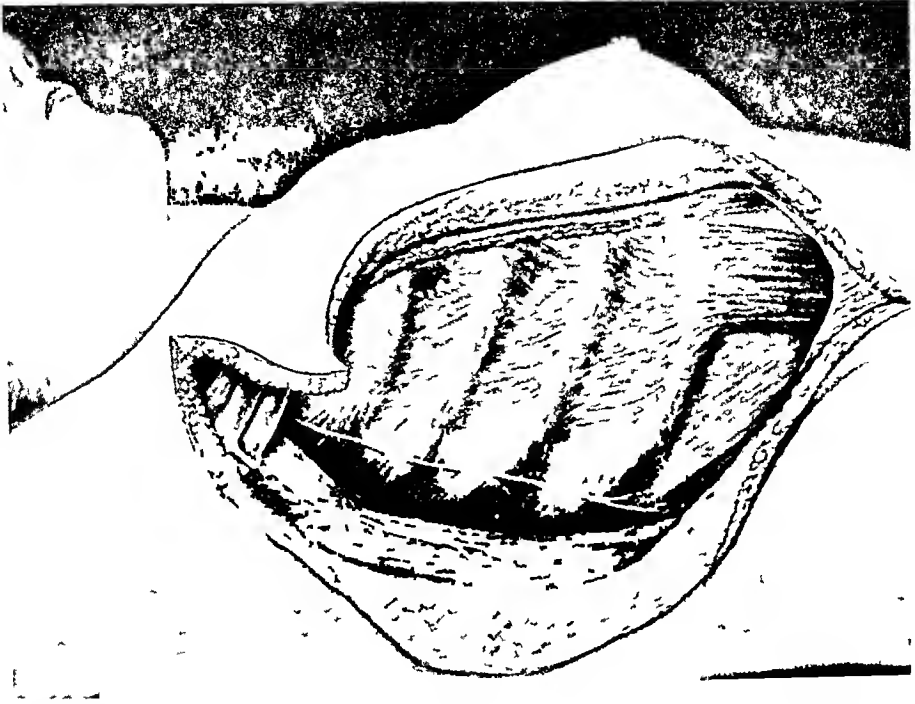


FIG 3—Entire breast with overlying skin and underlying pectoral muscles with axillary nodes and upper pectoral fascia on affected side removed. Undermining of skin carried over to midsternal line in front and to edge of trapezius behind.

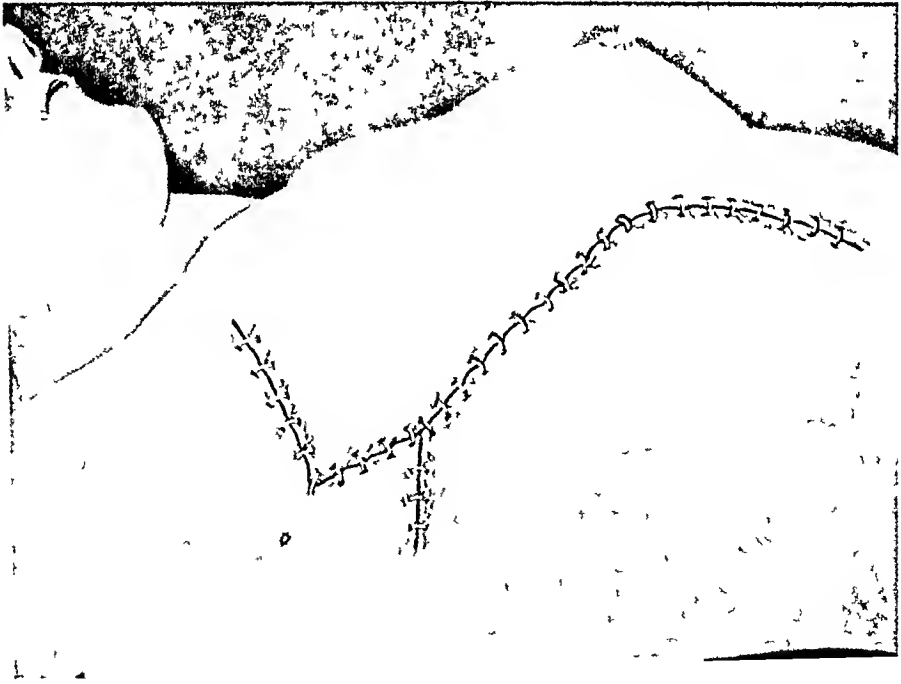


FIG 4—Wound closed—drain to axilla—extensive undermining makes grafting unnecessary.

SKIN REMOVAL IN BREAST CANCER



Figs 5 and 6 —A comparison of specimen as removed by Handley method (Fig 5 top) and by Rodman method (Fig 6 bottom) Note much greater amount of skin removed by Rodman method

Third, that with a properly planned procedure skin grafting is unnecessary except in the rarest instances

Fourth, that with such a procedure the usefulness of the arm on the operated side should not be impaired

Any operative method which should merit continued use must combine the steps in technic made necessary by the work of those who have given sound reason for them. We all accept as fundamental the work of Halsted and Handley, particularly. If the principles brought out by these and others can be combined into one procedure and if such a procedure can show as large a percentage of cures and eliminate certain undesirable sequelae it would seem that it should merit continued use.

W. L. Rodman in 1908 first advocated a method of radical breast amputation which he believed would meet these requirements. I believe that the method has more nearly done so than the original Halsted or Handley technics and that, therefore, it has deserved a greater usefulness than it apparently has had.

Some 65 years ago, the younger Gross (Samuel W.) was the first to show that wide skin removal was the first important step that should be made a part of the technic of breast amputation. At that time, D. Hayes Agnew, then Professor of Surgery at the University of Pennsylvania, remarked toward the close of his surgical career that he "had removed a cartload of breasts and never cured a case." Gross claimed that he was saving 95 per cent of his cases for three years.

They both were amputating the breast only. Agnew through the small elliptical incision, which removed a very small amount of skin and Gross using his "dinner plate" incision, removed all of the skin overlying the breast itself, allowing his wounds to granulate. It is interesting to see how each step added since then to the modern procedure resulted in definite improvement in results. Gross, continuing his interest, added an axillary dissection or at least what he thought was one, by extending from the top of his incision, a straight one to the axilla. The muscles were not removed and we know that, anatomically, it was impossible for him to have removed any more than the lowermost group of lymph nodes and fat at the base of the axilla. Nevertheless, his three-year cures were more than doubled—21.5 per cent. Sir Mitchell Banks, performing the same operation, had the same results—21 per cent. Bull of New York, performed a more thorough axillary dissection and had slightly better results—26.6 per cent three-year cures. In 1894 Halsted published his study of 50 cases, the first to be undertaken by the procedure which became a classic and which today is essentially the one most widely followed—at least in this country,—38.3 per cent were free from recurrence or known metastasis after three years.

In 1906 Handley published the first edition of his monograph on Cancer of the Breast. In a 2nd edition, published in 1922, he states that of 31 cases operated upon by his method, 48 per cent survived the three-year limit. In 1915, W. L. Rodman published the results of the first 50 cases operated

upon by his method. Of these, 72 per cent were well for three years and 24 or 48 per cent, for five years.

This method has been fully described elsewhere, and the details of the technic need not be gone into here. (W. L. Rodman's Monograph on Diseases of the Breast With Special Reference to Cancer—1908. A Lecture on Cancer of the Breast. Murphy's Clinic, Vol. IV, April, 1915). Suffice it to say that it has proven so satisfactory, over the years, that no changes have seemed necessary to add to it. As stated at the beginning of this paper, it is not our object to reemphasize all of the many accepted facts now amply proven by statistics and generally accepted. In reviewing many of the papers on this subject, I have been impressed, however, with the fact that from



FIGS 7 and 8—Showing usefulness of arms in a bilateral amputation. Scar does not touch arm, entirely on chest wall. No restriction of motion in abduction or full extension.

large clinics from which have come the most detailed and valuable statistics, these are based on the collected experiences of many operators, some of whom have been experienced, while others have added but a few cases to the study as a whole. This is true of both of the large series statistically studied and referred to in the beginning of this paper. In Haagensen and Stout's series only one of 36 operators had a sufficient number of cases to be of any statistical value. In the 35 years elapsing since the Rodman method was advocated, I am safe in saying that several hundred cases have been operated upon by this method by a small staff, the vast majority by either the originator of the method or myself at our clinic. I am prevented from giving a complete report of the results including private and ward cases by reason of the fact that many of the ward records were lost on moving them twice when the hospital was moved.

Even in the private records, some have proven impossible to trace and, therefore, could not be included in this study. I have been able, however, to trace 132 private cases, all operated upon by W. L. Rodman or myself.

61%	have been free from all evidence of recurrence for 3 years
46%	" " " " " " " " " 5 years
39%	" " " " " " " " " 5-10 years
16%	" " " " " " " " " 10-15 years
6%	" " " " " " " " " over 15 years

It has been our experience that the first two years is the critical period, and that very few died after five years (of cancer) Fifty-three-plus per cent had axillary metastasis at the time of operation—46 per cent did not Of those with axillary metastasis, 23.5 per cent survived five years or more Of those without axillary metastasis, 63.5 per cent survived five years or more A 46 to 48 per cent five-year survival, without any evidence of recurrence, local or distant, compares favorably with any statistics known to me (48 per cent W. L. Rodman, in 1915—and 46 per cent reported in this paper)

To finish this communication where we began, however, I repeat that a procedure yielding the statistics quoted is in general a more satisfactory procedure than others if, in addition, it eliminates certain undesirable sequelae In the 132 cases reported, a careful check of the records of those known dead and of the surviving patients themselves, have shown only three instances of local recurrence, or 2.2 per cent This method, therefore, all but eliminates local recurrences which, if they occur early must mean insufficient skin or fascial removal As stated, White, in his paper of last year, reported 22.6 per cent local recurrences in the Roosevelt series (Handley method)—Lewis and Rienhoff 19.2 per cent local recurrences (Halsted method), Haagensen and Stout 22.8 per cent Since 1908, not a single case has been skin grafted in our clinic In a few cases we have had a small part of the center of the wound slough In none of these has it been necessary to graft The original Halsted technic calls for skin grafting in the majority of cases, and I understand that this step is still almost the rule at the Johns Hopkins Hospital where the Halsted technic is still largely followed White reported 17 cases grafted in addition to the 238 cases closed by the Handley technic If this tremendous wound can be closed, not by a plastic procedure planned before the necessary radical steps are completed, the result is unquestionably better in that a pliable scar, not attached to the underlying chest wall, results More important than this, is the future usefulness of the arm on the operated side In scars resulting from the Halsted technic which I have seen, there is always a bridge of scar tissue from the chest to the arm, which results in distinct limitation of motion in abduction and extension This certainly undesirable sequela is unnecessary and should not be allowed to occur In our cases, the only limitation of arm motion is seen in the few instances which have developed marked edema Just why this happens, now and then, is another problem still not adequately explained We are of course, quite used to seeing transient and slight edema of the arm due, we suppose, to the lymphatic block When this becomes persistent, and marked, it may be due to this factor plus a mild type of infection resulting in scar tissue, as suggested by Halsted We make no effort to confine the arm after 48 hours and, in fact, encourage its use as the scar does not touch the arm and, therefore, is not in any way damaged when the arm is moved

No communication on this subject should be closed without paying tribute to the excellent work of others who have been especially interested

in it in recent years Auchincloss, of the Medical Center in New York, and Judd and Harrington, of the Mayo Clinic, particularly, have added valuable studies to it

CONCLUSIONS

- 1 Wide skin removal is important
- 2 That local recurrences are, at best, undesirable if they do not actually represent an inadequate eradication of the disease and certain of its known zones of local spread
- 3 That such local recurrences need not occur except in a very small percentage of cases (2.2 per cent with the method reported)
- 4 That skin grafting is unnecessary except in rare instances (none since 1908) by the method reported
- 5 That arm usefulness should not be impaired as a general rule and never unless marked edema follows
- 6 That a method advocated by W. L. Rodman, in 1908, meets these requirements, in addition to saving 46 per cent for five years from recurrence either local or distant, so far as could be demonstrated

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DISCUSSION—DR. DONALD GUTHRIE (Sayre, Pa.) I agree heartily with the points brought out by Doctor Rodman. As a matter of fact, I was one of the early enthusiasts of his father's operation, reporting it in 1914. We have used no other type of operation in our clinic since that time.

We believe that wide skin removal, with wide superficial and deep fascia removal are important and essential, for we are sure that skin recurrences come from the fascia underneath the skin and not from the skin itself. Our percentage of skin metastases has been very low, and it has been surprising how long some of these patients will live if these small skin metastases are removed, as they appear. As a matter of fact, I had one patient who lived nine years after the first appearance of metastasis, and who finally died of an hemiplegia. In our meager experience with this condition, the deeper metastases, through the lymphatic and vascular system, have not taken place.

It is surprising to me that these splendid principles embodied in Doctor Rodman's essay have not received more general wide adoption. For instance, the primary axillary section has so many points in its favor. We work from a clean into an involved area, the breast is handled far less than it is in any attack that centers itself upon the breast itself. The blood supply to the breast and to the muscles at the point of origin is controlled, and these operations are far less bloody than the usual operation which attacks the breast first.

Sometimes the condition of the axilla is found to be such that the operation had best be suspended. This was found in thirty of our patients upon primary axillary exploration.

Keeping the scar from the arm is also a most important thing, as is the anatomical, gentle, sharp dissection of the axilla. I am sure that some of the elephantiasis that occurs is due to a mild infection of the axilla which happens almost immediately postoperatively, and it is a factor in interrupting the return of the superficial lymphatics from the arm to the chest wall.

As I said, our number of metastases in the skin have been very small and, while we practice wide skin removal with fascial removal, it has been necessary to skin-graft but few of our cases.

Not to repeat any of the points brought out by Doctor Rodman, I would, however, like to call your attention to the extent of the skin incision, which includes the breast completely and is extended down on the abdomen so that the fascia of the recti can be removed. In the complete dissection with wide skin removal and wide fascia removal as well, the only two structures which are saved are the long respiratory and the subscapularis nerves.

In closing the wound in the center, it is important to use the tension approximation sutures, the far and near, we used to call it. We have found that an important factor in preventing loss of flaps is the "pic-crusting" of the skin, as first suggested by Charles Mayo years ago, to allow an immediate release of serum. If nonabsorbable sutures, either silk or cotton, are used and pressure is placed upon the main wound by a long commercial rubber sponge and another smaller rubber sponge is placed in the axilla, with the wound bound up tightly for four days, we practically have no serum collections of any kind. We have used cotton, with great enthusiasm, in almost all of our work.

The arm is mobilized quickly after the operation and this, I believe, is also a factor in preventing postoperative edema.

In following 409 of our 642 cases carefully, our figures agreed with those of Harrington, in that of those living five years, with no involvement of the axilla, there were 65.5 per cent, living ten years there were 40.9 per cent. With axillary involvement, at the end of five years there were 23 per cent alive, and at the end of ten years but 9.8 per cent were alive.

It is my belief that the reporting of a group of breast cases without separating those with axillary involvement and those with no axillary involvement at the time of operation leads us into a realm of false security.

DR J. SHELTON HORSLEY (Richmond, Va.) For many years I have been using the principle of the Rodman operation for cancer of the breast. It is a very satisfactory procedure, and usually the wound can be closed without skin grafting. It is important, of course, as Sampson Handley demonstrated many years ago, that the subcuticular tissue be removed in the block dissection and that but little subcutaneous fat and fascia be left in the adjacent flaps. Handley has shown that cancer spreads in a radiating manner in the subcutaneous tissue as well as through the main lymphatic trunks.

In addition, however, to the local precautions against recurrence for the last five years I have been removing both ovaries at the time of operation when the patient was within the menstrual age. It occurred to me, partly because of such work as that of Lett Beatson, and others, who performed oophorectomy in advanced cases of cancer of the breast with some apparent benefit, and also from beneficial results occasionally obtained by roentgenotherapy of the ovaries in cases of cancer of the breast, and the lowered incidence of cancer of the breast in mice after bilateral oophorectomy, that removal of both ovaries at the time of a radical operation for cancer of the breast would increase the cures. Since a large amount of estrogen appears to promote cancer of the breast, it would seem that elimination of the supply at the time of operation would give optimum results in preventing recurrence. Since beginning this procedure on November 19, 1937, up to January 1, 1942, I have performed 12 operations for cancer of the breast accompanied by removal of the ovaries in premenopausal women. Of the 12 cases, 11 were without recurrence at the last follow-up record in September, 1942. One died six months after operation from metastases to the lung and skin. These 11 cases have not, of course, gone through the five-year period, but the results are strongly suggestive. As a rule, in my experience most of the cases of cancer of the breast that recur, do so in the first 18 months after operation.

Huggins in his remarkable work on cancer of the prostate, has shown that roentgenotherapy of the testicles is not as efficient as excision and that the interstitial cells are not permanently destroyed by the roentgen ray. It would seem that this would apply particularly to the ovaries, because they are less exposed and more difficult to destroy by roentgenotherapy.

Three of the earlier patients, Mrs. C. D. A., Mrs. R. P. H., and Mrs. A. D. W.,

are cases with rather high-grade cancer. In one instance (Mrs C D A) the breast had been removed elsewhere, and there were metastases in the axillary lymph nodes. A radical operation was performed (Photomicrographs from these three patients shown)

DR STUART WILLIAM HARRINGTON (Rochester, Minn) I wish to congratulate Doctor Rodman on his presentation of skin removal in radical breast amputations and, also, on the excellent results he has obtained from the operative procedure. This is the lowest percentage of local recurrences that I have seen reported.

In the last review of cases which we have studied, our percentage of skin recurrence was approximately eight per cent. There are many factors which enter not only into the percentage of patients having skin recurrence but also into the prognosis as to life for patients who are operated upon for carcinoma of the breast, the most important of which are the extent of the disease at the time of operation and the type and grade of malignancy which are present.

Most surgeons have accepted radical mastectomy as the operative procedure to be utilized for carcinoma of the breast. The greatest variation in technical procedures has been in the type of incision to be utilized. This is important from the standpoint of local recurrence. I believe that the type of incision to be utilized must depend on the location of the growth in the different quadrants of the breast and also the type of breast, that is, whether it is a pendulous breast or a small breast attached to the chest wall. In a general way, if the tumor is in a twelve or six o'clock position or in the upper or lower quadrant, the vertical incision can usually be best utilized to make a wide excision of the growth. I always make the widest excision possible of the tegmental structures surrounding the tumor. If the tumor is in the three or nine o'clock position a transverse incision will often permit a satisfactory and more adequate removal of the tegmental structures surrounding the tumor. It is difficult to state in centimeters the amount of surrounding skin to be excised as this depends on the type of lesion, whether it is an ulcerating or an infiltrating type of lesion, but when possible an area of 7 to 9 cm from the growth should be excised. This is often difficult in lesions located in the extreme upper inner margin of the breast but an excision of this extent can be carried out in removing most of the axillary hair-bearing area and the wound can be closed without the use of skin graft by utilizing the latissimus dorsi muscle from the skin flap.

The majority of skin recurrences which we see occur in cases of ulcerating malignant lesions or the so-called inflammatory type of malignant lesion. In more than five per cent of our cases an ulcerating or inflammatory type of malignant lesion is present. Skin recurrence may occur even though a very wide excision of the skin has been made because the edema surrounding these lesions indicated malignant invasion of the skin and lymphatics. In cases of this type I have seen skin recurrence occur in distant areas such as the abdominal wall, back and scalp.

DR GEORGE J HUFER (New York) I do not intend fully to discuss Doctor Rodman's paper, but I cannot, without protest, accept his statement, that the Halsted operation results in such impairment of the function of the arm as to constitute a great disadvantage.

Doctor Rodman's statement that he has commonly seen function of the arm destroyed by a scar in the axilla following the Halsted operation is based, he admits, upon a few cases he saw at the Johns Hopkins Hospital in the very early days of this operation. Since that time the operation has been modified and improved, and I am quite convinced, from a very large experience, that the Halsted operation can be performed with a resulting axilla and with function of the arm quite as good as in any operation I have seen, including the Rodman operation.

The question raised by Doctor Rodman as to whether you shall skin graft or not skin graft perhaps deserves comment. One gets the impression from hearing men speak of skin grafting in connection with breast operations that skin grafting is a procedure which is either difficult or at least exceedingly objectionable. I do not think that such is the case.

One skin grafts in breast operations for a specific reason, and that is to secure closure of the wound without tension. It is a principle that is recognized, no matter where upon the body surgery is practiced.

If a surgeon chooses to remove so much skin—and I heartily agree with Doctor Rodman in everything he said about removal not only of a wide area of skin but also of subcutaneous tissue—that he can not subsequently close the wound without undue tension, then the only logical thing to do is to close it by means of skin grafting. I have had the opportunity in Baltimore, in Cincinnati, and in New York, of comparing, side by side, operations on the breast in which in one case skin grafting was used and in another case the skin was closed under tension, and I am convinced that a wound will be fully healed in a shorter time with grafting than with closure of the skin under tension.

DR CHARLES C LUND (Boston) There has been, as you know, a continuous interest in breast cancer in Boston, beginning perhaps in the nineties, or even earlier, with Warren, and then Greenough and Simmons of the Massachusetts General, and later Greenough, Simmons, Taylor, several others and myself, at the Huntington Memorial Hospital. Doctor Greenough was an advocate of the Rodman incision, and through his influence I was brought up to use it, and still use it, and like it. The work at both hospitals, has been published many times, and shows a long, continuous record of improvement. We feel strongly that any appreciable percentage of skin recurrence shows very inadequate planning of the operation or performing of the operation. I, personally, do not see why a Halsted operation would not give just as good results, if properly done, as described by Halsted, and reported on by Lewis and Rienhoff.

I do want to emphasize, though, the matter of choice of patients for radical breast operation. After roentgenograms of lungs, spine, pelvis and skull, exclusion from radical operation of any cases that have signs of metastasis there, and exclusion of cases with appreciable amounts of edema of the skin, or distant metastases of any kind. This all has been presented. The group working with Dr Whipple have published identical findings. After operation, with wide skin removal, I rather feel the way Doctor Heuer does, that a skin graft is not a disgrace, even if you use the Rodman incision.

TABLE I

132 Cases—Radical Mastectomies—Rodman Method

61%—Free from all evidence of local regional or distant metastasis for	3 years
46%—Free from all evidence of local regional or distant metastasis for	5 years
16%—Free from all evidence of local regional or distant metastasis for	5-10 years
6%—Free from all evidence of local regional or distant metastasis for	over 15 years

TABLE II

132 Cases—Radical Mastectomies—Rodman Method

53%—Axillary metastasis at operation
23 5%—Free from recurrence for 5 years
46%—No axillary metastasis at operation
63 5%—Free from recurrence for 5 years
3—Local recurrences in entire group—2 2%

DR WM CRAWFORD WHITE (New York) Last year, before this Association, I read a paper on "Skin Removal in Radical Mastectomy." I refer you to that paper for details. But I desire to call your attention to the fact that primary cases, with no axillary metastases, had a local recurrence rate of 10.8 per cent, while primary cases with axillary nodes involved had a local recurrence rate of 31.5 per cent. This is in accord with several other large clinics, whether or not skin grafting had been practiced. These reports are based on both private and ward cases, grouped together. Doctor Rodman has given us a very low local recurrence rate in 150 private cases. Apparently considerable skin has been removed, although his measurements are not stated. I am at a loss to explain his low recurrence rate.

I am an advocate of the removal of at least a minimum diameter of 15 cm of skin, but I am convinced that wider removal of skin will not reduce local recurrence. We must remember that Doctor Halsted practiced a wider excision of skin in his first 50 cases, yet he had a local recurrence rate of 31 per cent.

Local recurrence is due to cancer cells that have not been removed at the operation. We must remember that, in addition to the skin involvement in the neighborhood of the tumor, we have the other areas adjacent, in all directions, and, lastly, we must note the spread by lymphatic permeation and emboli to the intercostal and internal mammary

lymphatics These latter areas are not removed in the most radical operation, and are the source of retrograde growth into the overlying skin in many cases I think the last word on this has not been said

DR J STEWART RODMAN (Philadelphia, Pa, closing) I repeat, in closing this discussion, that I only had time in fifteen minutes to touch upon a very few problems concerning cancer of the breast All I was concerned with was the amount of skin removed, whether or not that bore any relationship or was important so far as local recurrences were concerned, whether local recurrences were unimportant or important, and whether the function of the arm had anything to do with the method of the procedure

Many other problems, some of which were brought out by the gentlemen who have spoken, and I am very grateful to them for taking part in this discussion, I did not have time to touch on I had to omit, toward the close of this brief paper, the matter of elephantiasis, or marked lymphadema of the arm With the Rodman method this does occur now and again I believe it occurs with any method that I know of, as far as that is concerned I do not know exactly why I think the combination of lymph blockage, with a mild infection of the axilla and arm resulting in scar tissue, may explain it, as suggested by Halsted

We often have to "pie-crust," as Doctor Guthrie brought out, in closing these wounds I think that pie-crusting is very useful in the procedure It does seem to relieve a good deal of lymphatic block or of venous stasis at least, of the skin edges

Occasionally we do get, even though it is always possible to close these wounds by extensive undermining of the skin, necrosis of the skin edges This is never marked enough to require grafting to close the defect I insist that this is not a plastic procedure It is simply a closure of a wound made at a time when you do not know whether you are going to be able to close it or not, because you have removed enough skin in doing so

As I see it, the objection to skin grafting is the resulting fixation of the scar to the chest wall, the fact that it is time-consuming, and, in our experience, is an unnecessary addition to the operative technic

As to Doctor Horsley's discussion, there are many problems concerned that I did not go into, one of which is the matter of sterilization We have tried that We are still undecided as to whether it is of any value or not

Of course, we all know of the tremendous amount of work that Doctor Harrington has done, and the beautiful results he has obtained I, personally, have had no luck whatsoever with acute skin cancer The cases he showed on the screen would be what I call cancer "en cuirasse" I do not know what he calls it, but to me that has been hopelessly fatal business

I think the location of the growth, of course, is very important, as to where you plan your skin incision, but, nevertheless, we find with a skin incision such as we showed on the screen as the Rodman method, you can keep away from the edge of the growth, depending where it is, by varying the upper and lower line of the incision We do not have to change the type of the incision depending on the location of the growth

Now as to Doctor Heuer's remarks, I was very much pleased to hear him say what he did I have never had the pleasure of seeing Doctor Heuer perform a breast amputation, and I am afraid I am a little old-fashioned in going back to my student days at Hopkins I was not an undergraduate student there, but I was doing graduate work in pathology when Doctor Heuer was the resident in Surgery Doctor Halsted, I recall very well at that time showed some 15 to 20 cases he had done by his method Of course, that was the original procedure No doubt it has been improved by Doctor Heuer, and others But in the cases shown not one could get her arm above a right angle because of the bridge of scar tissue from the chest to the arm

I have seen other cases since then, done by this method, and by good surgeons, that also could not get their arm above a right angle

I do not believe that it is not possible to avoid this complication All I said in my paper was that the cases I have seen done by Halsted's method resulted in a certain amount of impairment of the usefulness of the arm in abduction and extension, that unless marked edema occurs such limitation of motion never follows the Rodman technic

PILONIDAL CYSTS AND SINUSES*

MAJOR FRANK C SHUTE, JR, M C, MAJOR THOMAS E SMITH, M C,
LT COL MAX LEVINE, SN C,

AND

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THE HIGH INCIDENCE of pilonidal cyst or sinuses in members of the armed forces has resulted in this lesion becoming a major surgical problem in all military hospitals. In civil life, disability following treatment is usually not great, as the patient carries on his usual occupation during the greater portion of the healing period. A soldier on the contrary, cannot undergo the extraordinary exertion of military duty with an unhealed wound. Healing often requires months with the loss of many man-days.

In spite of much research, the etiology of these sinuses is not clear. Stone²³ notes a similarity to the preen gland of certain birds. Kallet¹⁸ suggests an embryonic rest of a vestigial secondary sex gland. Tourniaux²⁴ Herrmann²⁴ Mallary,²⁵ and Gage¹⁶ believe the cyst results from an abnormality in the development of the neural canal. Fieele¹³ and Fox¹⁵ stress an embryonic infolding of cutaneous epithelium. Kooistra²⁰ found evidence to support each of the latter two theories and states that no conclusive opinion seems justifiable.

There is also a great divergence of opinion regarding treatment. Among the ambulatory methods, the aim is to destroy the diseased tissue by physical or chemical agents. Anderson¹ injected chloride of mercury, Crookall⁹ silver nitrate, Biegeleisen,² fuming nitric acid. Cutler and Zollinger,¹⁰ and, later, Block and Green³ report successful results with a modified Carnoy's solution. Smith,³¹ and, later, Turell²⁵ used roentgenotherapy on recurrent cases with good results.

Kleckner,¹⁹ in 1936, by means of a questionnaire from members of the American Proctologic Society, collected 4699 cases. Of these 4,231 had been operated upon by the open method indicating that this was the method of choice among experienced proctologists. Cauteiv excision and open packing was first recommended by Stanton³² Rogers and Hall²⁸ and, more recently Rogers and Dwight²⁷ have reported gratifying results with this method.

Following excision, closure of the wound has been advocated by many. Due to the difficulty of obliterating the dead space and of approximating the tissues, numerous methods have been described. Ferguson and Mecray¹⁴ use a mattress suture of steel wire tied over a gauze roll on either side. Bungess⁶ undermines the wound edges and uses silk retention sutures tied

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over a sponge or gauze Gage¹⁷ stressed the value of sea sponge pressure to obliterate the dead space Recently, Dunphy and Matson¹² described a method of undercutting the overlying tissue from the sacral fascia to facilitate closure

Lahey,^{21, 22} after block excision, filled the defect with a pedicle flap obtained from over the gluteus maximus Later he modified this procedure by using a flap attached at both ends allowing the defect of the gluteal region to granulate Cattell⁷ used a similar procedure but closed the space over the muscle by converting it from a crescent into a Y

Brezn⁴ in order to remove the scar from the midline, used a U-shaped incision circumcising the openings of the sinuses within the U A pedicle flap was then reflected and the cyst and sinus tracts dissected out

MacFee,²³ and De Pizzio¹¹ recommend a partial closure, suturing the skin edges without tension to the sacrococcygeal fascia This leaves a small raw area which heals by granulation Colp,⁸ in 1929, and, recently, Van Alstyne³⁶ described a similar method except that the skin edges were in approximation Buie⁵ does not remove the floor of the sinus overlying the fascia and sutures the skin edges to the membranous edges of the sinus This subsequently undergoes a squamous metaplasia

Recently good results have been reported by numerous military surgeons with various methods of treatment Among these are Pickett and Beatty,²⁶ using excision and packing, Woldenberg and Sharpe,³⁷ excision and primary suture, Scott,³⁰ using buffered sulfanilamide locally with primary suture, and De Pizzio,¹¹ employing the skin to fascia type of operation

A survey of these cases, in the Eighth Service Command, by Colonel Coley, the Surgical Consultant, revealed no uniformity of opinion as regards treatment the great desirability of improving end-results, and the necessity of reducing morbidity In studying the material of the Brooke General Hospital, as a part of the above survey, it was found that from January to October, 1942, there had been 77 cases treated by surgical excision Fifty-six had healed and returned to duty, while 21 were still under treatment

Of the 56 healed cases half of them had electrosurgical excision, and the wound packed, while the remainder were excised and closed by primary suture

In the 28 cases closed by suture, 12 healed primarily in an average time of 19 days Sixteen cases became infected with subsequent opening of the wounds From then on, these were treated by packing and healing occurred in an average of 69 days

In the 28 cases treated by open packing, the average time of healing was 77 days (Fig 1)

The study indicated a lower average healing time for the closed case subsequently breaking down than for the case treated by the open method In addition, the average healing time of all closed cases was 47 days as compared with 77 days for the open method

On October 16, 1942, the closed method was adopted for all cases Excision was by scalpel Meticulous attention was paid to hemostasis

Cotton or wire suture replaced catgut Great care was taken to avoid undue tension and to eliminate dead space Pressure dressings, as advocated by Gage,¹⁷ were employed

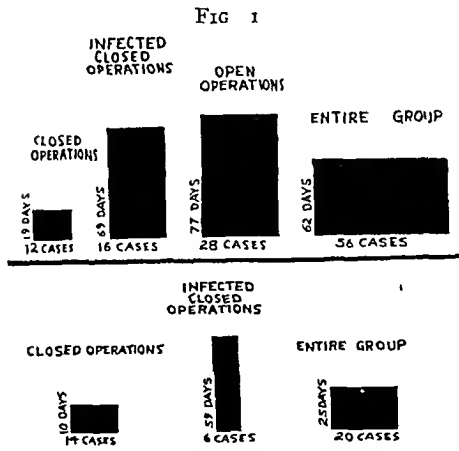


FIG 1—Average healing time of cases between Jan 1 and Oct 1, 1942

FIG 2—Cases treated by excision and primary suture

Twenty cases were treated according to this plan. Fourteen healed primarily in an average of 10.5 days. Six had postoperative infections, and healed by second intention in an average of 59 days. Cotton and steel wire were each used in 50 per cent of the cases. It seemed as if the wire wounds were superior (Fig 2).

At this time, a new method of closure suggested itself to one of us (Frank C Shute), which seemed to eliminate the difficulties of dead space and tension. A double elliptical incision is made in the skin surrounding the cyst and sinus tracts, and is carried down perpendicularly to the gluteal aponeurosis on either side. The block of tissue is dissected off the sacrococcygeal fascia and removed (Fig 3). A lateral incision is now made through the gluteal fascia on either side, corresponding to the original skin incisions and is carried well into the muscle (Fig 4). This creates an inner fibromuscular flap which is turned medially and sutured to its fellow of the opposite side. This fills in the area dorsal to the sacrum and coccyx eliminating the dead space (Fig 5).

Cutting the fibers of the gluteus maximus mobilizes the lateral flaps so that it slides medially over the edge of the sacrum and can be sutured to the opposite lateral flap without tension (Fig 6). The skin now falls together and is easily approximated (Fig 7).

This method satisfactorily overcomes the difficulties of tension and dead space which are inherent in the other types of closure. In addition, the transplanted muscle furnishes an abundant blood supply to the base of the wound which is of great importance in healing.

Fifty-nine white males have been operated upon according to this technic. Most were in the third decade of life. The two outstanding symptoms were pain and discharge, while the objective signs were inflammatory induration, abscess or sinus formation. Not a single asymptomatic case was operated. Fourteen had abscesses which were immediately incised. The excision followed in an average of 8.6 days. Ten were recurrent cases and were prepared for an average of 5.6 days before operation. Thirty-five presented chronic infected sinus tracts and were prepared an average of 3.5 days. All cases were placed at rest and given hot sitz baths. No pre-operative sulfa drugs were used. In some of our earlier cases the sinus tracts

PILONIDAL CYSTS AND SINUSES

FIG 3

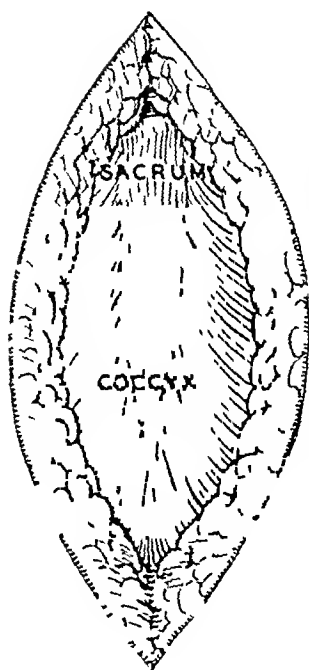


FIG 4

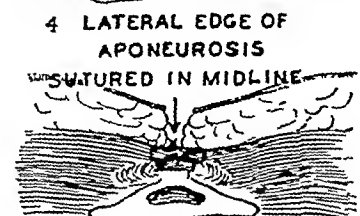
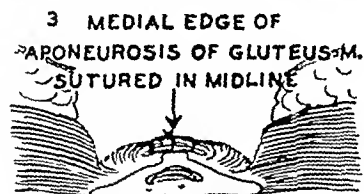
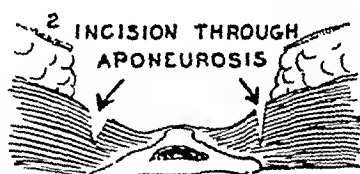
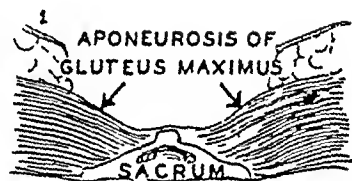
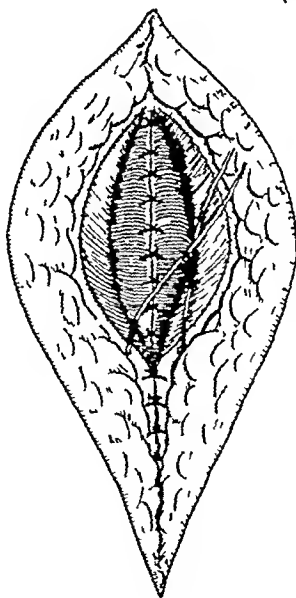
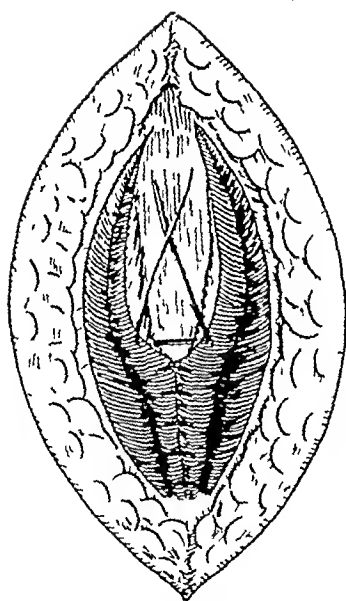
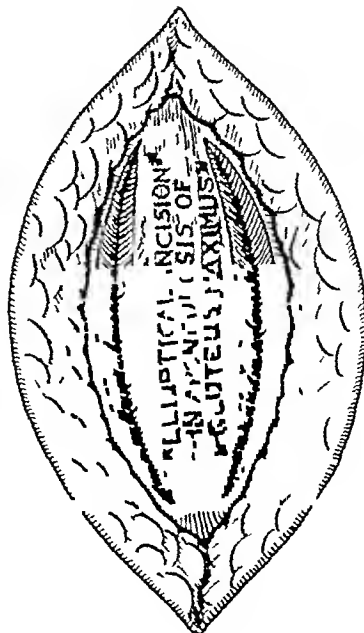


FIG 5

FIG 6

FIG 7

FIG 3—The sinus has been excised exposing sacrococcygeal fascia and the aponeurosis of the gluteus maximus

FIG 4—An incision has been made on either side through the aponeurosis of the gluteus maximus. It is not necessary to join the incisions at the ends of the ellipse

FIG 5—The inner fibromuscular flaps are being sutured together in the midline

FIG 6—Approximation of the outer muscular flaps

FIG 7—The steps of operation in cross section

were injected with methylene blue but we found, as did Rogers²⁸ in which the dye filled the lymphatic trunks and gave a false impression as to the extent of the lesion

The block of tissue removed usually measured about 12 x 8 cm. The largest block was 15 x 10 cm. In this case, the wound closed easily. Sinus tracts extending into the thigh were dissected out separately from the midline block in a few instances. The bacteriology of the lesions were carefully studied. The excised specimen was brought to the laboratory in a sterile towel. Its skin surface was saturated with alcohol which was then ignited. An incision was made into the infected area and a loopful or two of material was streaked on eosin-methylene blue agar and tubes of lactose broth were inoculated for the determination of coliform organisms. Blood agar plates, tubes of thioglycolate broth and milk and beef heart infusion broth were inoculated for other organisms. The routine blood plate procedure was found to yield 46 per cent negative findings whereas thioglycolate broth or skim milk yielded 95 per cent positive findings of streptococcus and staphylococcus infections. The latter media were very satisfactory for organisms which required more or less anaerobic conditions.

Thirty-nine specimens were examined and the following types of organisms were encountered

(1) No organisms found	2
(2) Streptococci (hemolytic—3, nonhemolytic—8)	11
(3) Staphylococci (hemolytic—6, nonhemolytic—7)	13
(4) Mixture of staphylococci (predominantly hemolytic) and streptococci	8
(5) Anaerobic streptococci	5
(6) Coliform bacteria	None

In the specimens from recurrent cases, no epithelial tissue was found. Only sinus formation as a result of infection in a dead space was noted. This is in keeping with Rogers²⁹ findings, and we believe the majority of so-called recurrences are the result of incomplete obliteration of dead space.

Postoperatively, these patients were given paregoric for three days then mineral oil. Enemata were administered as indicated. Patients were allowed to be ambulatory as desired at the end of 12 to 24 hours. The sutures were removed on the fifth to seventh day. Pressure dressings were abandoned because they were unnecessary with this operation. They seemed to cause invagination of the suture line.

The results in these 59 cases are most gratifying. Forty-eight healed in an average time of approximately eight days. Eleven cases had postoperative complications. Three were accidents and eight infections. One patient fell out of bed, opened his wound on the fifth postoperative day. Another had a fecal impaction, and separated the lower one inch of his wound on the sixth postoperative day. The third, an unusually active man, opened an inch of his wound on the second postoperative day. These were pulled together with adhesive and healed in 15, 16 and 15 days, respectively.

Of the eight suffering infections, three were minor stitch abscesses and five were infections of the lower perianal angle of the wound. These infected cases healed in an average time of 22 days. The healing time for the entire group was approximately 11 days. When healed, the enlisted men returned to duty after an average convalescent period of three weeks, while officers returned in 16 to 20 days following operation (Fig 8).

The distributions with respect to time for healing are given in Table I, and curves showing the cumulative per cent of cases healing after various periods following operation, for the uncomplicated infected and the combined series of cases are shown graphically in Figure 9.

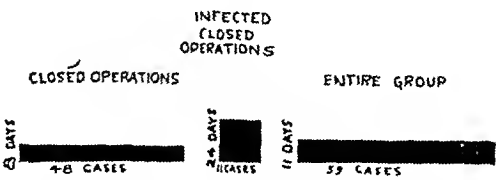


FIG 8—Cases closed by new technique

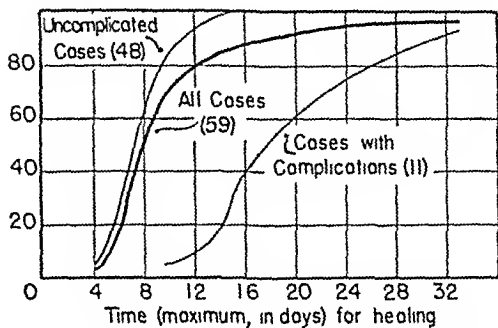


FIG 9—Curves showing cumulative per cent for periods of healing after excision of pilonidal cysts

TABLE I
PERIODS FOR HEALING AFTER EXCISION OF PILONIDAL CYSTS

Time for Healing in Days	Uncomplicated Cases		Infected Cases†		All Cases	
	No	%	No	%	No	%
3 to 5	3	6.2			3	5.1
5 to 7	13	27.0			13	22.0
7 to 9	21	43.6			21	35.6
9 to 11	8	16.6			8	13.5
11 to 13	2	4.5	1	9.1	3	5.1
13 to 15	1	2.1	2	18.2	3	5.1
15 to 17			2	18.2	2	3.4
17 to 19			1	9.1	1	1.7
19 to 21			1	9.1	1	1.7
21 to 23			1	9.1	1	1.7
23 to 25						
25 to 27			1	9.1	1	1.7
27 to 29						
29 to 31			1	9.1	1	1.7
Over 31			1*	9.1	1*	1.7
Total	48		11		59	
Average time		7.8		21.8		10.6

† Includes three cases which sustained accidents
* Fifty-three days

In the series of 48 uncomplicated cases, it will be noted that 90 per cent were healed in less than 11 days, and all of them in 15 days or less. Even in the 11 cases in which stitch infections or other complications occurred, 70 per cent were healed in less than 23 days and 90 per cent in less than 30 days. For the entire series (59 cases) it will be noted that 60 per cent were healed in as short a period as nine days, 80 per cent in 13 days, and 90 per

cent in 17 days. The period of healing extended beyond 25 days in less than five per cent of cases, the latter including one case which required 53 days and another 30 days.

No 38-gauge stainless steel wire was used in the wound for ties, and No 32-gauge wire for sutures. In our hands wire has produced less reaction in tissue than catgut or cotton. It is not used on account of its supposedly great tensile strength. As a matter of fact, the finer grades break readily if undue tension is applied. In the skin around the perianal region a subcuticular suture of wire is very satisfactory. In the remainder of the wound interrupted sutures were used.

Buffered sulfanilamide was used in the first 29 cases. It seemed to cause an excessive amount of oozing and serum in the wounds. Nine of the 11 complications occurred in these cases. In the latter 30 cases, in which sulfanilamide was not used, there occurred only two complications.

An accurate evaluation of end-results must, of course, await a more extensive employment of the method and the passage of further time. However, the many advantages of the operation, and its ready adaptability to war conditions, has led to its presentation at this time. None of the 59 cases have, so far, returned with a recurrence.

SUMMARY

The experience with pilonidal cysts and sinuses at the Brooke General Hospital is reviewed.

An operation is described which is found to be far superior to any previously used by the authors. A wide, double elliptical incision is carried perpendicularly downward to the fascia of the gluteus maximus. The circumscribed tissue block is separated from the sacrococcygeal fascia and removed. A lateral incision through the gluteal fascia in the line of the original incision is now made on either side. It is deepened into the fibers of the gluteus maximus and the fibromuscular flap thus created is turned medially and sutured to its fellow of the opposite side, in the midline.

This fills in the area dorsal to the sacrum, eliminates the dead space, and furnishes an abundant blood supply to the base of the wound. The lateral flap slides medially over the edge of the sacrum and is sutured to the opposite lateral flap without tension. The skin is now easily approximated.

Results of this technic in 59 cases are presented. Forty-eight healed primarily in an average time of eight days. Eleven cases had postoperative complications, and healed in an average time of 22 days. The healing time of the entire group was 11 days.

Bacteriologic examination of 39 excised cysts disclosed viable organisms in 95 per cent of the specimens. Nonhemolytic streptococci and hemolytic staphylococci constituted the predominating flora, in five instances only anaerobic streptococci were found, and it is interesting to note that coliform bacteria were absent.

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DISCUSSION—DR HARVEY B STONE (Baltimore) Ever since Doctor Finney demonstrated a case of pilonidal sinus to my third-year class at the Medical School, I have been interested personally in this curious and provocative lesion. It certainly has been, in the last few years, provocative of a remarkable outpouring of publications, but that has not always been true. It was only about 16 or 18 years ago that I read a paper on this subject before the Southern Surgical Association, reporting a group of some 60 cases, and after the meeting was over, several widely experienced surgeons told me that they had known little or nothing about pilonidal sinus before and did not believe they had ever recognized a case, and several, not quite so frankly, said they did not believe that I had seen as many as I had reported.

I do not believe that the latter doubt will exist in anybody's mind now, after the numerous publications have come in and after the experience of Induction Boards and army surgeons with the really wide prevalence of this lesion.

There are a number of interesting problems—its embryologic origin, the reason for the defect in embryology which produces it, and the difficulty from the practical, clinical side in securing rapid, firm, and enduring healing after removal.

It is with the latter problem that Colonel Burch's paper deals, and I think there are at least three recognizable causes of trouble in securing desirable results. One is infection, and his emphasis on the spending of some time preparatory to operation in cleaning up an infection I think is a point of very great practical importance. A second is the complete and adequate removal of the lesion itself. A third is the dealing with the resultant wound.

So great has been the difficulty in dealing with the wound that a number of writers on the subject have frankly abandoned any attempt to close it and advocate that it be dressed open and left open to heal by granulation. Others have gone further, and have even abandoned attempts at excision and treat the lesion by some method of chemical or electrical destruction, in order to avoid an open wound altogether, and a great many have published papers describing various methods of plastic closure or suture, designed to obliterate the dead space.

This paper of Doctor Burch's I think falls clearly in this last group. Personally, I believe that closure should be undertaken, and that it is an unnecessary surrender to pack it open and wait for it to granulate. The reason that I feel so is because, as the statistics of Doctor Burch have shown and those of others who have advocated somewhat different plastic closures have indicated, where closure is attempted a considerable percentage of primary successes are obtained. That is "all to the good," and even where closure fails, and where the wound then has to be treated as an open wound and allowed to fill up by granulation, the period of deferred healing is probably less than if no attempt at closure had been made in the first instance.

So I believe we should accept the principle of an effort at closure, and that that effort entails some plan to obliterate the dead space. The dead space has a noncollapsible, bony floor. It has edges which are difficult to approximate without tension. Therefore, the introduction of any principle which will overcome these difficulties, which will help to close the dead space and bring together the wound edges in proper position for healing, so that they are neither inverted into the depth of the wound nor under great tension in being approximated, is highly desirable and is, I think, the sound principle to proceed on.

I think that Doctor Burch's method is ingenious, and that it is based on fundamentally sound conceptions. He certainly has presented a laudable record of success so far, and we all hope that he, and others, will give this method wider employment and report further as to its success.

DR FRANK H LAHEY (Boston) I wish to speak, just briefly, about this subject because, being responsible for a little of the literature, I feel interested I feel particularly interested, however, because of recent inspections of Naval hospitals, and in the course of the inspections seeing pilonidal sinuses in Army hospitals and seeing the number of duty-days saved by primary suture

I came yesterday from the United States Naval Hospital in Norman, Oklahoma There, in the Surgical Service they have now excised 15 consecutive pilonidal sinuses, with average hospitalization of 19 $\frac{5}{8}$ days

I recently saw the Torney General Hospital in Palm Springs, California, an Army hospital, where Doctor Beaver had had 14 consecutive pilonidal sinuses treated by excision, closure averaging, again, under 3 weeks

In my mind, the problem is quite different for the men in the service and for those in civilian life In the service the important thing is man-hours, but equally important is beds When one realizes that Doctor Beaver reports his series as averaging 19 days' disability, and the Naval Hospital at Norman, 15 days, that the Navy and the Army are seeking additional beds, and that these patients, unlike those in civilian hospitals, occupy beds until surveyed to duty, this is, I believe, in the Army and Navy quite a different problem from that in civilian life

Just now I spoke to Doctor Cattell because he has been interested in pilonidal sinuses in civilian practice The plan of Horatio Rogers in Boston, who advised the plan of local excision, is applicable in an office or in an out-patient department If these people are so situated that they can get away from their work or their school long enough to obtain this daily or alternate-day treatment, then I feel that the method of local excision with granulating in, is permissible The Army has a different problem, however, and has demonstrated, I think, in many of the military hospitals that excision will work, does save hours, and certainly does save beds

DR HENRY F GRAHAM (Brooklyn) I was recently stopped by a man who wanted to inquire about his son He said his son was in the Army and he had had three operations upon the base of his spine, but he knew they must have been good operations because they were all done by Majors I am sure it was not performed by Colonel Burch

There is one little step that I have employed, that I think, in some cases, perhaps only in civil life, is of value in diminishing the infection at the time of excision It is something that can be done in addition to these steps that have been recommended by Colonel Burch, and which seemed so sound and good to me I am going to try his method

I often use an electric cutting current and make a vertical incision through the infected cyst or sinus, laying it wide open It is then wiped out, the edges are held apart, and, with a bipolar current and a heavy, round-tipped needle, I fulgurate the base of the wound until the entire lining of the cavity has been destroyed to a depth of about one-eighth of an inch Then, when it is entirely dry and the infection theoretically has been mostly eliminated, the excision is made

I see no reason why that could not be done first, and the method of Doctor Burch used after that, if you do not carry bipolar fulguration so deep as to destroy the underlying tissues This will destroy a great deal of infection, and our results have been much better since we have used this method than when we undertook simple excision

DR JAMES M MASON (Birmingham, Ala) The renaissance of pilonidal sinuses and cysts has been extremely interesting After years of only casual comment, the subject has been given a prominent place in surgical literature by the large number of cases that have been reported during the past six months

My attention was first directed to this anomaly by a paper that Harvey Stone presented at the meeting of the Southern Surgical Association in 1923 He stated that "less than a dozen original articles had been found in a fairly extensive search covering the previous sixty years" The literature since the appearance of Stone's publication has been singularly barren of contributions until within very recent months Beginning about November, 1942, reports, from Army hospitals particularly, are appearing in

increasing numbers. These reports discuss the management of the large numbers of pilonidal sinuses that are applying for treatment in Army hospitals in all sections of the country.

A review of the discussions of the embryology of the sinus is interesting. As far back as 1892, Mallory came to the conclusion that the sinus resulted from failure of obliteration of the caudal canal. This view had been previously expressed by Hermann and Teureux, and other European investigators. Stone has not accepted this view and holds to the theory that the sinus results from a "special local downgrowth of epithelium originating from the true skin and not from the medullary groove."

In 1935, two noteworthy publications appeared, one by I. M. Gage, *Archives of Surgery*, August, 1935, entitled "Pilonidal Sinus: An Explanation of its Embryological Development", another by S. L. Fox, *Surgery, Gynecology & Obstetrics*, February, 1935, entitled "The Origin of Pilonidal Sinus, With an Analysis of its Comparative Anatomy and Histogenesis." Gage supports the theory of failure of obliteration of the medullary canal. Fox upholds the theory of downgrowth of epithelium. Ewing, discussing tumors and anomalies in the sacrococcygeal region says that "the entire group is not only numerous but complicated, and a rigid classification is at present impossible" (*Neoplastic Diseases*, Fourth edition, page 1006).

Regardless of views concerning embryology, surgeons recognize that cure should be sought by excision and closure of the wound.

Another matter of surprise is that with large numbers of young men in college taking part in football, baseball, and every sort of athletic activity, the cyst has attracted but little attention nor, so far as I recall, did it give rise to any material trouble among the troops in World War I. Of course, the same relative numbers of pilonidal sinuses among a given number of individuals should not differ from time to time. Army surgeons claim that the extreme activity carried on in the training period is responsible for the infections and abscesses that bring the soldier to the hospital for medical attention.

Stone and Gage have advocated excision and closure, after proper preparation. They have, likewise, directed attention to the difficulty of completely obliterating the dead space at the bottom of the wound and of the value of compression in assisting in this obliteration. Looking at the illustrations of Colonel Burch's ingenious operation, it seems to me that there must still be a dead space underneath the flaps of gluteus muscle and that a pressure dressing should still be employed to obliterate.

COLONEL JOHN C. BURCH, M.C. (closing). The success of this operation depends upon filling up the dead space by means of flaps derived from the gluteus maximus muscle. Mobilizing the medial flaps, likewise, mobilizes the lateral flap and allows them to slide in readily.

The wound must be absolutely dry. Nonabsorbable sutures are preferred. Thirty-eight-gauge stainless steel wire for ties and No. 32-gauge for sutures has proved very satisfactory.

One cannot be too careful about infection; it can nullify any operative technique. Most of our complications come from operating too soon. The best preventive for infection is an adequate preparation of the patient.

Our experience with sulfanilamide has been quite interesting. In the first 29 cases, we used a buffered sulfanilamide. It seemed to cause oozing and the accumulation of serum in the wounds. Nine of the 11 complications were in this group.

EFFECTS OF ETHER AND CYCLOPROPANE ANESTHESIA UPON THE RENAL FUNCTION IN MAN¹

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SEVERE ACUTE ACID-BASE EQUILIBRIUM DISTURBANCES and changes in the regulation of body water exchange are seen too frequently during the post-operative period. They occur in spite of seemingly well directed fluid therapy. Although it is generally recognized that alterations in renal function are responsible for many of these changes, the etiologic factors and the specific changes in kidney function that are involved must be known before therapeutic measures can be employed objectively to correct them and to prevent them.

In an attempt to determine whether the anesthetic agent that was employed had any direct effects upon the kidney, renal blood flow and filtration rates were studied simultaneously in human beings preoperatively, during or immediately following operation (patient anesthetized), and in some instances postoperatively.

METHODS—Seven patients who were to be operated upon under ether anesthesia and four who were to be operated upon under cyclopropane anesthesia were selected for study. The operative procedures were varied (Tables I and II). No attempts were made to alter the routine preoperative or operative procedures. To establish a normal for each individual, preoperative inulin and diodrast studies were run before each operation. About an hour before the operation, a hypodermic injection of morphine and scopolamine was given. A solution of 5 per cent glucose was administered during the operations. Inulin and diodrast studies were started near the end of the operation and were carried through the recovery stage.

The inulin and diodrast clearances were carried out, respectively, according to the technique of Alving, *et al.*,² and Smith, *et al.*,⁴ as modified by Foà and Foà.³ Two Gm. of inulin and 5 cc. of a 35 per cent solution of diodrast were injected intravenously. Fifteen minutes were allowed for this to mix thoroughly in the blood. The bladder was then emptied of urine and the clearance period was started. Two blood samples were obtained at ten-minute intervals. The clearance period lasted for 30 minutes and, at that time, the bladder was again emptied and washed. From the blood and urine concentrations, the clearances were computed. In those cases where changes

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Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

were encountered, attempts were made to obtain postoperative studies. These were carried out one week after the operation. All the cases were adequately hydrated and were in acid-base equilibrium, as far as could be simply determined. All anemias had been corrected and no significant cardiac disease was present. All individual temperatures, during the studies, were within normal limits.

RESULTS—Figures 1, 2, and 3 illustrate the variations in renal blood flow and filtration rates under ether anesthesia (Consult Table I for data that is not included in these figures)

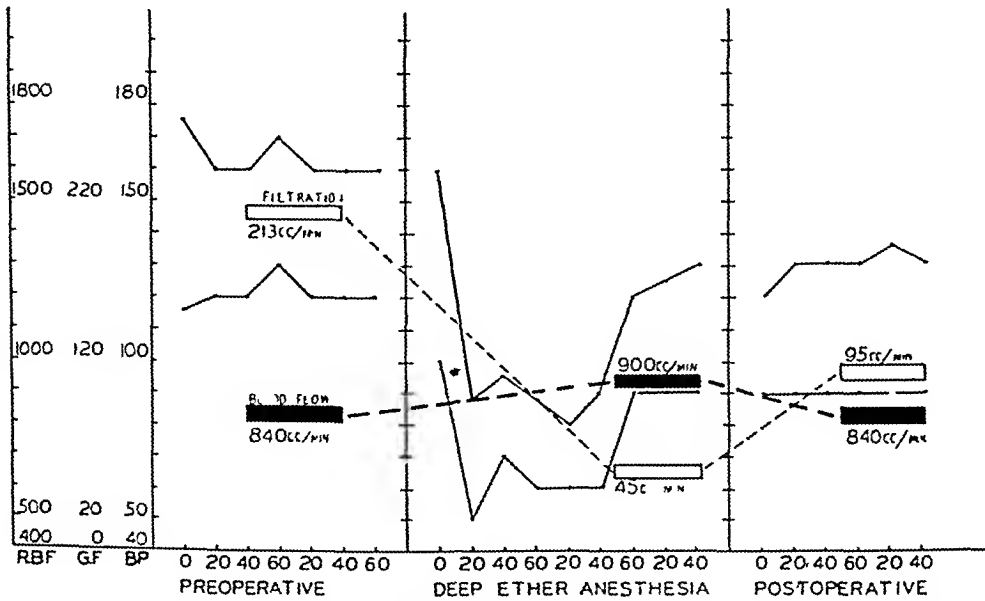
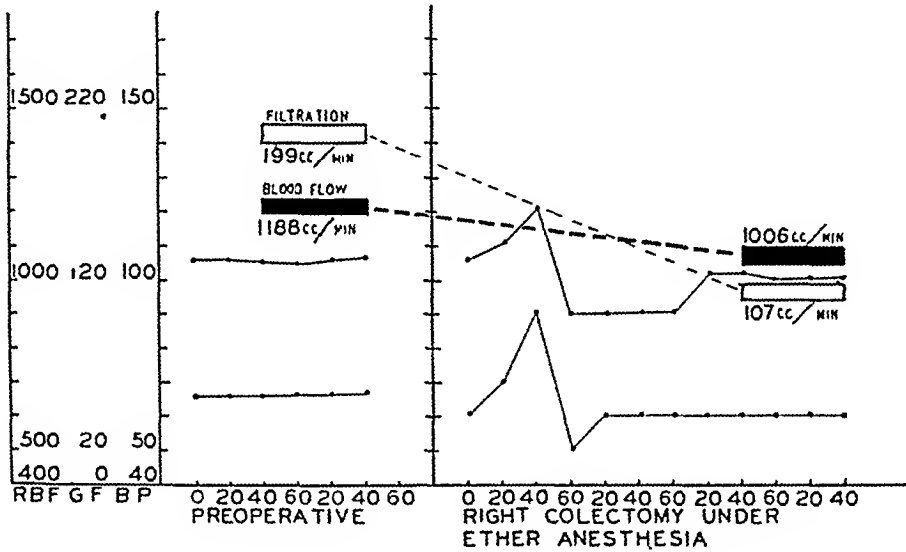
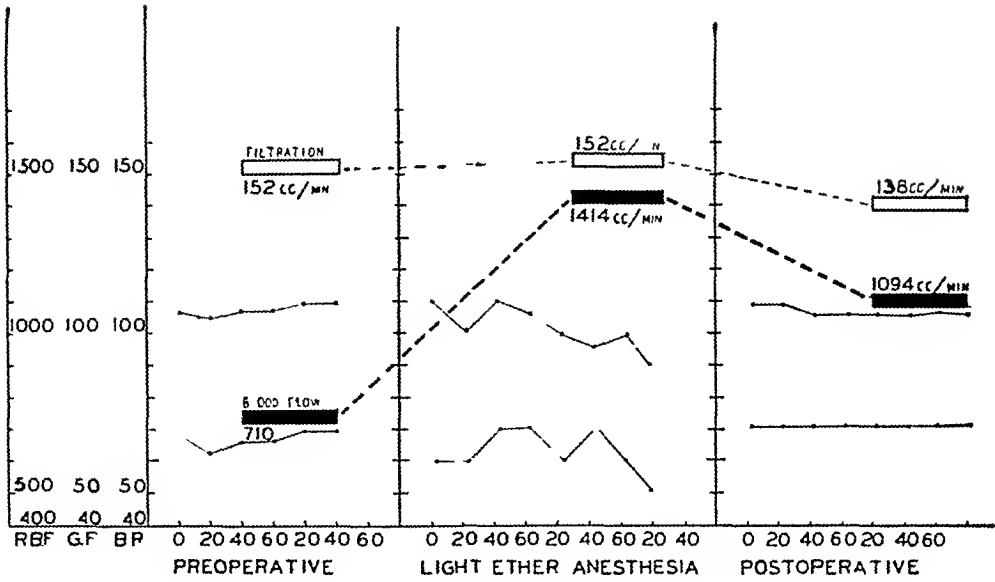
TABLE I

Case	Sex	Age	Type of Operation and Duration	Anesthetic Agent	Preoperative or Postoperative	Average Blood Pressure	Effective Renal Blood Flow, Cc/Min	Filtration Rate Cc Plasma/Min	Filtration Fraction C _i /C _p %	Tubular Excretory Mass mg 1 Per Min	Total Filtration 30 Min	Urine Excreted 30 Min	Per Cent Reabsorbed
No 1 A M	F	33	Combined A P resect of rectum	Ether	Preop Operat	105/65 100/60	1187 8 1006 4	198 6 107 8	22 8 18 7	54 6	4958 3234	570	80 5
No 2 M H	M	37	Combined A P resect of rectum	Ether	Preop Operat	125/80 120/70	1449 1 1369 0	138 3 140 7	19 2 19 8	64 3	4149 4221	355 36	91 4 99 2
No 3 E B	F	45	Hernia	Ether	Preop Op Postop	105/70 90/50 110/70	710 0 1414 7 1094 0	152 6 152 7 138 4	34 7 17 4 20 2	24	4578 4581 4152	294 76 250	90 3 98 3 94 0
No 4 J M	M	33	Plastic 3 hrs	Ether	Preop Op Postop	120/90 125/90 120/70	680 9 852 0 839 5	80 6 110 0 101 7	21 1 21 5 19 9	34 6 36 5	2418 3300 3051	385 38 420	84 1 98 8 86 2
No 5 J H	M	62	Hernia 2 hrs	Ether	Preop Preop Op Postop	170/120 165/100 90/60 170/105	785 0 844 0 900 0 841 5	224 3 213 0 45 1 95 0	53 1 47 8 9 3 20 6	33 7 31 5 38 0	6729 6390 1353 2850	46 5 300 85 424	99 3 95 3 93 7 85 1
No 6 R S	F	58	Resection rt colon 4 hrs	Ether	Preop Op Postop	160/90 120/70 170/100	1045 7 817 0 810 0	140 3 47 2 232 0	20 0 8 5 36 4	30 6	4209 1416 6960	416 20 402	90 1 98 6 94 2
No 7 M	M	54	Suprahoid 3 hrs	Ether	Preop Op	120/80 120/80	740 1 1230 6	73 7 122 0	19 6 19 8	31 3	2211 3660	236 56	83 9 98 5
No 8 M	M	36	Total gastrectomy	Avertin-ether	Preop	110/75 90/50	725 5 18 4	126 3 1 1	32 8 10 7	27 8	3789 33	338 17	91 1 48 5

Four patients of variable ages, weights, and sex, who were anesthetized for periods of time varying between one and four hours, suffered no significant changes in either renal blood flow (diodrast clearance), or filtration rate (inulin clearance) as a result of anesthesia and operation. The low preoperative blood flows in two cases (Cases 3 and 7, Table I) are considered to be due to nervous factors during the first determinations. This concept is supported by the subsequent observation that the postoperative flow was normal (Case 3, Table I). Therefore, the increases in renal blood flow (Cases 3 and 7) between the preoperative and the operative determinations are not considered to be experimentally significant. Two patients (Cases 1 and 5, Table I) suffered diminution in the rate of glomerular filtration without a fall in renal blood flow. One (Case 5) experienced a sustained decrease for one week following his operation.

During, or immediately following, thoracoplasties performed under cyclo-

EFFECTS OF ANESTHESIA ON KIDNEY



FIGS 1, 2 and 3—The effects of ether anesthesia upon malin and diodrast clearances in man

propane anesthesia, glomerular filtration rates decreased significantly in all of the patients studied (Figs 4, 5, 6 and 7, and Table II) Renal blood flows were variable, two increased (Figs 4 and 5) and two decreased (Figs 6 and 7) One of the increased flows was observed while blood and pulse pressures were lowered (Fig 5) The two patients in whom decreased renal blood flows were noted had low blood and pulse pressures during the tests (Figs 6 and 7) In one instance (Fig 7) "total" renal failure occurred The urinary outputs, in spite of large amounts of intravenous and oral fluids, were low during the first 24 hours postoperatively (Figs 5 and 7)

TABLE II
CYCLOPROPANE SERIES

CYCLOPROPANE SERIES																			
Case	Sex	Age	Type of Operation and Duration	Preoperative Operative Postoperative	Urine Volume in Cc	Sodium MEQ	Liter	Chloride MEQ/Liter	Ammonium MEQ	Liter	Total Nitrogen Gm Liter	Inulin Mg /Liter	Inulin Clearance Glomerular Filtration Rate Cc /Min	Diodrast Iodine Clearance Cc /Min	Effective Renal Blood Flow Cc /Min	Total Filtrations 30 Minutes	Urine Output 30 Minutes	Per Cent Reabsorption	
No 1 FW	M	40	Lateral thoracoplasty, 1 3/4 hrs	Preop Operat	136 35	12 74	1 5	14 85	6 4	0 997	1,309 11,180	120 78	6 7	750 502	0 0	1,225 2,361	3,618 136	610 96	83 8
No 2 BM	M	22	Second stage T P L, 2 1/4 hrs	Preop Operat	610 12	22 6	6 2	14 7	33 5	3 157	24,593 1,509	83 1	1 3	614 758	0 0	1,100 1,239	2,493 4,599	16 46	98 99
No 3 PS	M	45	Second stage T P L, 2 1/2 hrs	Postop Operat	46 25	63 3	9 6	45 11	39 5	11 080	17,552 14,572	153 75	3 6	758 1,824	0 0	1,239 1,051	4,599 2,268	46 25	99 98
No 4 PB	M	23	First stage thoracoplasty 3 hrs	Postop Operat	330 44	10 73	9 0	15 113	3 2	1 33	2,664 8	125 1	1 4	636 50	0 8	1,051 98	3,753 135	330 44	91 67

* Prodromal shock cases, 3 and 4

The one patient who had an ether-aveitin anesthesia (Case 8, Table I) showed a severe decrease in both renal blood flow and filtration rates Further observations on the effects of aveitin-ether and aveitin anesthetics are now in progress

DISCUSSION —The inulin (glomerular filtration) and diodrast (renal blood flow) clearances of a comparatively large number of patients who are operated upon under skilled ether anesthesia do not decrease (Table I, Cases 2, 3, 4, and 7) In two instances (Cases 1 and 5 Table I), the filtration rate decreased with anesthesia but renal blood flow was not changed significantly The lower filtration rate during anesthesia in Case 1 (Table I) was still within normal limits However, in Case 5 the filtration rate declined 78 per cent, and was far below normal immediately following the operation One patient (Case 6) suffered significant falls in both the rate of filtration and renal blood flow during the operation

In view of the relatively large number of patients who showed no significant changes in inulin or diodrast clearances during light or moderately deep anesthesia, even though the anesthesia was prolonged, it is felt that any changes that occurred in glomerular filtration rate and in renal blood flow (tubular excretion of diodrast) during operation under ether anesthesia, were probably the result of factors other than the possible primary action of the anesthetic agent upon the kidney parenchyma It is probable that in one instance (Case 5, Table I) a severe vasomotor control derangement due to an overdose of ether was the direct cause of the relatively

severe and prolonged reduction of the filtration rate. The operation was simple, a bilateral inguinal herniorrhaphy, and blood loss was minimal. The low operative filtration rate existed concomitantly with low blood and pulse pressures. The fall in pulse and blood pressures occurred while an inexperienced anesthetist was carrying the patient in plane 4, S III*. What part his mild hypertension may have played in the picture is unknown. His urine did not contain blood, casts, or albumin. The significant decreases in both renal blood flow and glomerular filtration rate in Case 6 (R S)

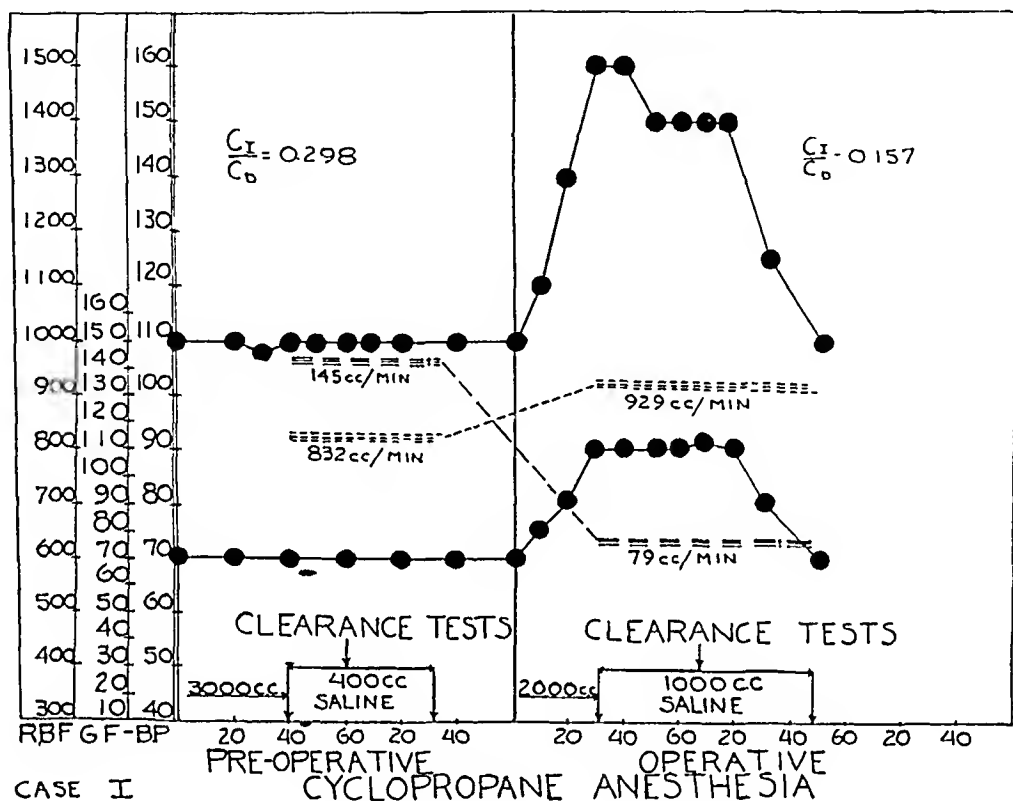


FIG 4

were possibly due to an acute blood volume reduction incident to an extensive and prolonged operation.

The observation that the glomerular filtration rate fell in all of the patients studied during cyclopropane anesthesia, regardless of renal blood flow or blood pressure changes, seems to indicate that a direct effect of the anesthetic agent upon vasomotor mechanisms may be responsible for these changes. However, in this series of experiments no data pertinent to acid-base equilibrium are available. Without such data one cannot rule out the possibility that the respiratory acidosis, which is usually associated with cyclopropane anesthesia, may have been directly responsible for the diminution in the glomerular filtration rates, especially in those cases in which renal blood flow increased.

There is no evidence in either group of observations that anesthesia blood volume flow reduction or other variations from the normal incident

* Plane 4, S III denotes surgical anesthesia with complete intercostal paralysis

to surgery effect any changes in the reabsorptive capacities of the renal tubules. The fraction of the glomerular filtrate reabsorbed by the tubules was either the same or greater during anesthesia than the controls in all patients except two (Case 8, Table I and Case 4, Table II). The respective urinary ionic and nitrogen concentrations in the preoperative and operative urines of Case 8, who suffered a decrease in the reabsorption fraction of glomerular filtrate, are not known, so that no statement can be made regarding tubular function. However, in Case 4 (Table II) the concentrations of the sodium ion, the chloride ion, ammonia nitrogen, and total urinary nitrogen

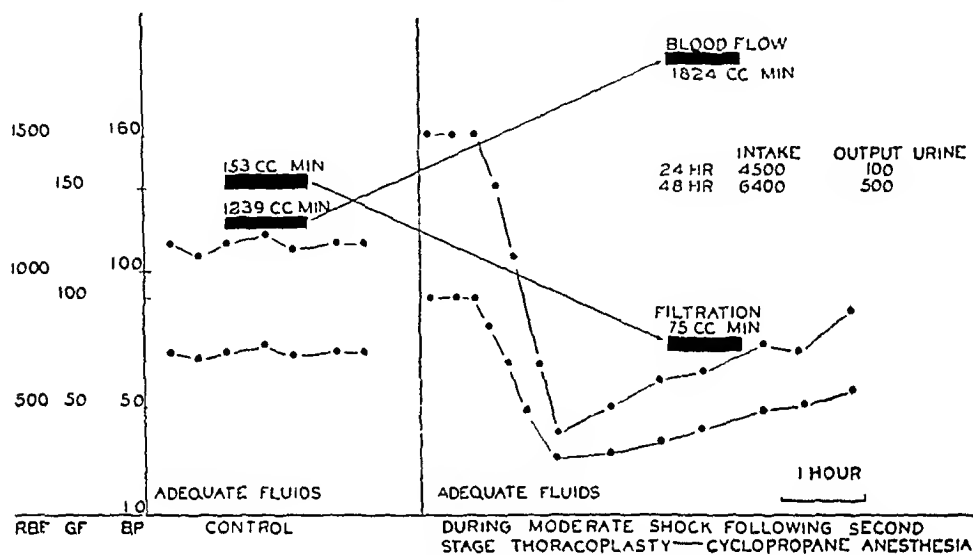


FIG 5

were 66, 7, 8, and 78 times greater during the period of low fractional reabsorption (anesthetic period) than they were during the postoperative period of high reabsorption. The urine flow during the latter period was seven times greater than it was during the former. Therefore, although granting that these relationships may be fortuitous, since no attempt at balance control was made, it is probable that no great decrease in tubular reabsorptive capacity occurred during anesthesia in this instance, although the fraction of glomerular filtrate reabsorbed decreased, because the ionic and nitrogen concentrations and urinary flows underwent equivalent reciprocal changes. The relatively high concentration of ammonia nitrogen in the urine collected during anesthesia from Case 4 (Table II) indicates that the tubular cells retained their capability of effecting deamination of amino-acids and, therefore, were still capable of a considerable base saving—a tubular function of importance—in spite of anesthesia and a very low renal blood flow. Also, it is of interest that glomerular capillary permeability was not grossly increased by anesthesia or reductions in renal blood flow because no albumin or red blood cells were found in the operative or postoperative urines.

The lack of evidence for a gross increase in glomerular capillary permeability, for decreases in tubular excretion and reabsorptive capacities, or for

an increase in tubular permeability during ether and cyclopropane anesthesia, indicates that the variations in glomerular filtration rates and urinary outputs during and following the administration of these anesthetic agents are probably due, in the greater part, to primary derangements in acid-base equilibrium, in body water and ion distribution, and in cardiovascular functions incident to anesthesia, blood loss, and visceral trauma. Therefore, direct solutions of the problems concerned with the maintenance of homeostasis, especially in regard to acid-base equilibrium and renal function, during

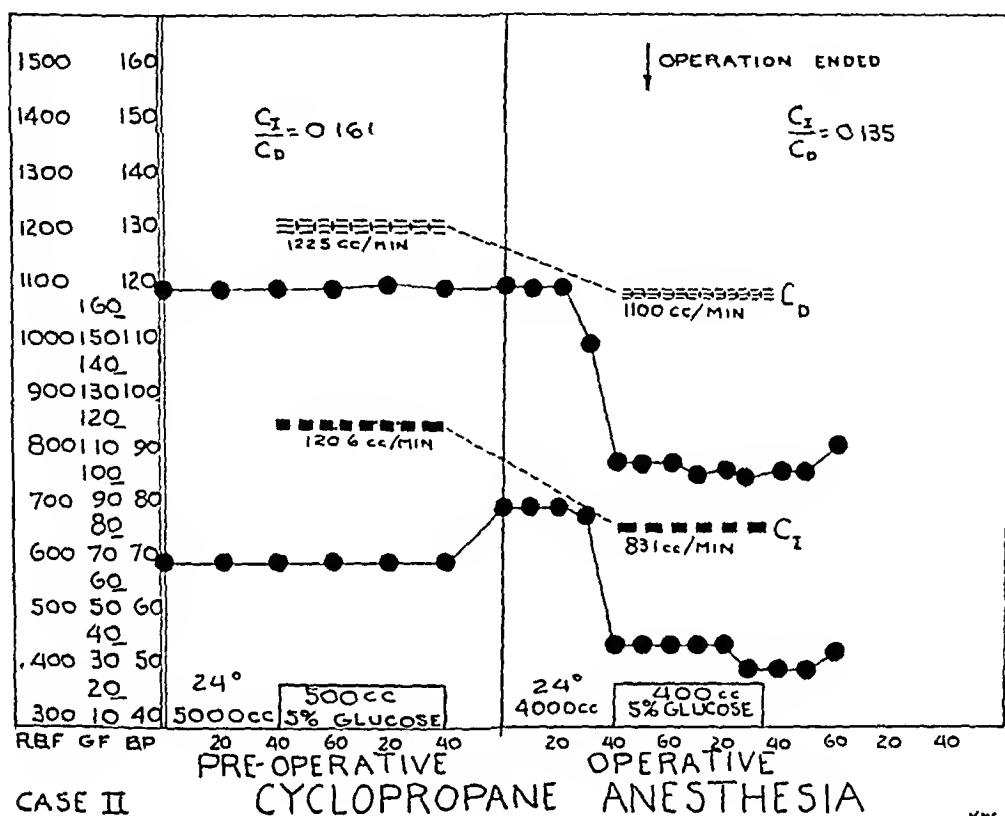


FIG 6

and immediately following operations performed under ether and cyclopropane must await further studies of water and ion distribution, and acid-base balance in man under conditions that pertain to anesthesia and surgery. Although the solutions to these problems will necessitate the expenditure of a great deal of effort and time, it is likely that they will be more practical of solution than they might have been should ether and cyclopropane have a direct effect upon the kidney parenchyma.

CONCLUSIONS

1 Inulin and diodrast clearances are not affected by ether anesthesia provided that the anesthesia is well controlled and significant blood volume reduction does not occur.

2 The inulin clearances of all the patients studied were depressed during cyclopropane anesthesia, the simultaneous diodrast clearance changes were variable, two increased and two decreased during anesthesia.

4 Because of the failure to demonstrate any deleterious action of ether or of cyclopropane upon the kidney parenchyma, the variations in glomerular filtration rate and renal blood flow, that occur during anesthesia, are probably, in great part, due to a combination of the "extrarenal" actions of these agents and the operative procedures. The disturbances in acid-base

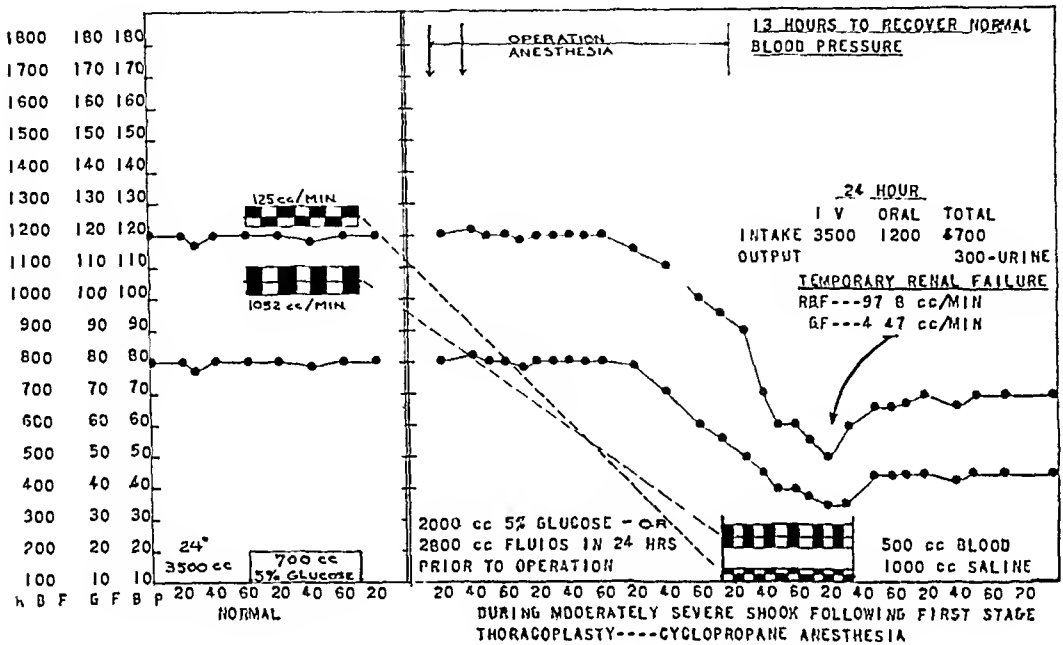


FIG 7

equilibrium, body water and ionic distribution, ionic concentration, and cardiovascular function, that are associated with disease, anesthesia, and surgery, are considered to be the primary causes for postoperative oliguria (See the appended summary of earlier experimental work regarding the effects of anesthesia upon kidney function) *

Pingale, *et al* (1905) Ether Oliguria, depression of sodium and nitrogen excretion
Brit M J, 2, 542

Hawk (1911) Ether Oliguria, elevation of NPN for 5-14 days in some cases
J Biol Chem, 4, 321

Miller and Cabot (1915) Ether PSP excretion in 335 patients—average depression
—20%, with fairly rapid recovery Arch Int Med, 15, 369

Mac Nider (1920) Ether 131 dogs—43 became either temporarily or permanently
anuric Related to age, fatty infiltration in kidneys No response to diuretics unless
“glucose protection” had been afforded J Pharmacol and Exper Therap, 15, 249

Luckhardt and Lewis (1923) Ethylene Safe from standpoint of not producing anuria
J A M A, 81, 1851

- Marx (1931) Chloroform, Ether, Chloral Hyd Edema more easily produced in animals by infused salt solution if anesthetic is given J Pharmacol and Exper Therap, 41, 483
- Walton (1933) Amytal, Avertin, Ether Recovery of diuresis slowest after barbiturates J Pharmacol and Exper Therap, 47, 141

5 The observations reported concerning the effects of ether upon kidney function are in agreement with the earlier observations of Smith⁷ concerning the effects of spinal anesthesia upon renal function

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See also Miller, B F, Alving, A S, and Rubin, J Jour Clin Invest, 19, 89, 1940
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- ⁵ Smith, H W, Rovenstine, E A, Goldring, W, Chasis, H, and Rooges, H A The Effects of Spinal Anesthesia on the Circulation in Normal Unoperative Man With Reference to the Autonomy of the Arterioles and Especially those of the Renal Circulation Jour Clin Invest, 18, 319, 1939

DISCUSSION DR FREDERICK A COLLER (Ann Arbor, Mich, closing) As Doctor Moyer stated, there are many things that we do not know about this whole problem, and we do hope this is a start on the final elucidation

There is no question but that, usually, in the healthy person these alterations in kidney function are unimportant and the patient goes merrily on to recovery Occasionally, however, the depression of kidney function that may be associated with prolonged anesthesia, prolonged operation, and perhaps the associated loss of blood may well be important, and even be the cause of death

In the presence of certain states, that we can briefly summarize as malnutrition where there is hypoproteinemia, or profound or even moderate anemia—these abnormalities in kidney function may be accentuated I wish to present two cases in which the administration of the wrong kind of parenteral fluid nearly led to the death of the patients

Case 1—G B, age 36, had had a subtotal hysterectomy The operation was performed under nitrous oxide-ether anesthesia, the anesthesia was carried for four hours During the day of operation and for the first four postoperative days one liter of saline solution was given intravenously in addition to 2500 cc of other fluids (water by mouth and 5% glucose by vein) On the fifth postoperative day she began to vomit, and gastric drainage was instituted 2500 cc of saline solution were given daily in addition to 2500 cc of 5% glucose solution for the next five days During this later period her distention increased rapidly, urine flow decreased, respiratory difficulties appeared, and peripheral edema was noted On the tenth postoperative day her condition approached *citricis*, and it was decided to pass a Miller-Abbott tube into the duodenum through a gastrostomy Upon opening the abdomen four liters of ascitic fluid was obtained, and her distention was relieved This fluid contained 2.79 Gm % of protein (a/g ratio of 1.71)

For the next four days her urinary output exceeded her oral water intake, and her edema disappeared She recovered

The amount of salt that was given to her would be readily handled by a healthy individual but she could not do so. Why? We believe that the following physical abnormalities were collectively responsible: 1. Anemia (Hb —54% S), 2. hypoproteinemia, and 3. operative obstruction of the right ureter.

The parenteral administration of salt solution in the face of these variations from normal resulted in a general deposition of fluids in tissues and body cavities. The deposition of fluid in the body cavities was associated with a large loss of serum proteins; in fact, she had as much serum protein in her abdominal cavity as she had in her blood stream ($4,000 \times 2.79 = 11,160$ Gm in the ascitic fluid) and $1,750$ (calc plasma vol) $\times 5.4 = 9,450$ Gm in the blood vessels. This finding is particularly interesting in that it is fundamentally similar to Blalock's observations concerning the effects of parenteral saline given to animals in shock.

To summarize, this case illustrates the protein "washing out" effect of relatively small amounts of saline solutions when given in the face of anemia and hypoproteinemia. We cannot say what part the acute reduction in renal function that was associated with the acute obstruction of the ureter and the prolonged anesthesia played in this picture.

Oftentimes one sees a picture as that which follows. Case 2—A man in good health had a five-hour anesthetic, and he reacted very well afterward. The total water intake for the first day was within normal limits, but the urinary output was low. The first day he passed only 200 cc of urine. This oliguria was probably in greater part due to the prolonged anesthesia. The next day he passed 1500 cc of urine, a mild diuresis that is commonly seen on the second day following ether anesthesia. However, in spite of this diuresis, there may not then have been enough urine put out in the first two days to care for the excretion of his phosphates and his sulphates, which have preferential rights of excretion over the chlorides, and so chlorides that may have been given in slight excess during these two days would tend to be retained.

The following day he became distended, began to vomit, and had liquid stools (We find that saline retention is a very common cause of distention and of vomiting). His urine was now 400 cc, in spite of the fact that intake had been forced up. The following day he became irrational, and the salt and glucose solutions were greatly increased (5100 cc—[2,500 of saline]) to cover the losses from the gastro-intestinal tract, with the result that his urine dropped down to almost nothing.

We then gave a liter of sodium lactate $\frac{M}{6}$, and within eight hours he had excreted 1150 cc of urine, and 14 hours after the sodium lactate was given he was eating and drinking, and was fully rational.

There are seemingly two types of retention of fluids. We think that both of these stormy postoperative courses could have been avoided had we been more cautious in the use of the salt solution. I think I can give one or two rules that we are now following that enable us to avoid these complications which occur during the post-anesthetic period and occasionally in those who have not been operated upon—the anemic, the malnourished, and the nephritic.

Do not give salt solution unless there is a definite indication for its use. This means that the patient must have lost salt before you see him, *e.g.*, as a result of vomiting, diarrhea, fistula, sweating, *etc.* We prescribe it with the same care we prescribe any potent drug, such as digitalis or morphine. We think it is unwise to give salt solution for three days, at least, after operation, unless there is a very definite indication for its use. If salt solutions are to be given it is necessary that a nearly normal urine flow be established before the injection is begun. To establish a urine flow glucose solutions are used.

According to the very outstanding work of Wolfe, of the University of Rochester, it now looks as though, if one wishes to replace salt losses, it is wise to give salt solutions not as normal salt solutions but as solutions of five-tenths per cent or less.

DISCUSSION—DR ALFRED BLALOCK (Baltimore, Md.) This paper of Doctor Collier, Doctor Moyer, and their associates, is an important one. It is rather disturbing to learn of the difficulties that one may encounter with the administration of normal salt solution.

A great deal of attention has been focused on the kidneys in recent years. All of us are familiar with the work on hypertension as produced by the Goldblatt method. Much interest has been displayed in the renal failure that may occur after crush injuries and after burns. In connection with crush injuries the most interesting recent comment is that of Bywaters, to the effect that one should ignore the shock that may appear early and should promote diuresis by giving large quantities of fluid before the renal blood flow is speeded up by the giving of plasma or blood. Now Collier and Moyer, and their associates add to the interest of surgeons in the kidneys by their important observations on the effects of anesthetic agents.

Although the kidneys are not very large organs, approximately one-fifth of the total cardiac output passes through them. Most tissues in the body react to a decreased blood flow by extracting increased portions of oxygen from the blood. Such is not the case with the kidneys unless the blood flow decreases greatly. In other words, the renal vein oxygen content remains high and the A-V difference small, except in dire emergencies. In other words, in shock the oxygen consumption of the kidneys is decreased much more than in most tissues. This may have something to do with the observations that have been reported today.

On the other hand, Moyer has stated that damage may occur in connection with anesthesia even when the renal blood flow and blood pressure are little if any affected. The explanation of their findings is not apparent. One would not expect anoxic anoxia to arise from the use of cyclopropane. Possibly, but not likely, histotoxic anoxia may be caused. It is possible that anesthetic agents produce harm by reducing the pulse pressure. Perhaps Doctor Moyer will comment on whether this occurs. As regards treatment it is apparent that one should give a fluid such as glucose solution where the glucose could be metabolized and the water will be available for excretion by the kidneys.

DR CARL A. MOYER (Ann Arbor, Mich., closing) I will answer Doctor Blalock's question first. The decreases in glomerular filtration rate during cyclopropane anesthesia seemingly have little relationship to the systemic pulse pressures, decreases in filtration rate were noted with elevated as well as with lowered pulse pressures. In fact, diminutions occurred during periods that were characterized by an increased renal blood flow, an increased mean systemic blood pressure, and an increased pulse pressure.

We have no objective explanation for the above phenomenon. It is possible that intrinsic renal changes in capillary filtration pressure might have taken place that overshadowed the effects of the systemic elevation of pulse pressure and the increased renal blood flow. It is also possible that deformations in the various fluid compartments of the body that are incident to anesthesia might be responsible for some of the diminution in filtration rate. There is a mild hemoconcentration and a minor decrease in blood volume associated with cyclopropane and ether anesthetics, this would tend to decrease the effective glomerular filtration pressure provided that renal capillary pressure remained unchanged. Should the decreases in glomerular filtration rate that are associated with cyclopropane anesthesia (without hypotension) be due to the relatively small changes in osmotic pressure of the blood that are associated with anesthesia, it will be necessary to grant that the physical state of the blood that is being supplied to the kidney has more to do with the rate of glomerular filtration than has been suspected.

THROMBOSIS AND EMBOLISM^{*}

REVIEW OF 202 PATIENTS TREATED BY FEMORAL VEIN INTERRUPTION

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THE RELATIONSHIP of venous thrombosis and pulmonary embolism has long been established. Postoperative pulmonary complications frequently ascribed to other causes have been due to infarct. The source of emboli has been generally considered mysterious and often no sign of thrombosis was apparent prior to the fatal episode. This state of affairs has brought about an attitude of great fear concerning the possibility of sudden death during illness or following surgical procedures but has been accepted as an unavoidable sequence of events in a small percentage of cases. Although pulmonary embolism in the presence of well-defined thrombophlebitis has been understood, there have been many sudden deaths due to embolism the source of which remained obscure. Gradually, there has come about a better understanding of the problem and the radical methods for reducing the morbidity and mortality.

Thrombophlebitis is apparently more common in some geographic localities than others. It seems that there is greater frequency of this disorder in New England than in the deep South. Perhaps this discrepancy is due to the same climatic variance commonly known regarding respiratory tract infections. Ochsner¹ has popularized the term "phlebothrombosis," which signifies a noninflammatory lesion. Homans² prefers the term "bland thrombosis," and both refer to a condition of venous thrombosis not associated with inflammation. This type is insidious in onset, produces little warning of pain, swelling, and fever, so that the condition is not suspected until infarct occurs. The thrombus in this instance is nonadherent to the vein and is easily dislodged. It is in these cases that we have our most serious problem and greatest number of deaths from pulmonary embolism. In true thrombophlebitis with pain, swelling, and fever the thrombus is more or less fixed to the wall of the vein by the inflammatory process and although it is well known that embolism occurs in this variety, it is in fact less likely than in the nonadherent type.

Although the source of infarct and fatal embolus have been correctly supposed to come from the veins below the vena cava in thrombophlebitis there has been a slow recognition of the fact that pulmonary embolism may occur in apparently well and afebrile patients. Pelvic veins have been accredited with the focus in many cases and often veins in the neighborhood of the

^{*} Read by title before the American Surgical Association, May 13-14, 1943 Cincinnati, Ohio

would have been suspected. Although infarcts may arise from these smaller veins, it is now believed that they are infrequently the source and never produce a sudden, massive fatal embolus. The heart has long been known to harbor thrombi, particularly in the auricles during or following fibrillation. Doubtless, a small percentage of fatal emboli do have their origin in the right heart.

Piettim¹ found that 133 out of 144 fatal emboli, studied by him, originated in the region drained by the inferior vena cava, and 91 of these patients had involvement of the femoral or iliac veins.

Hampton and Castleman⁴ have demonstrated the clear-cut roentgenologic picture of infarct and have made it possible to diagnose this lesion with great accuracy. They have further shown that 95 per cent of all emboli exclusive of heart origin can be traced to the leg veins. These thromboses usually start in the veins of the calf muscles and propagate into the larger veins of the leg. The long, straight femoral vein can harbor enough thrombus to completely occlude the pulmonary artery if it becomes free at one time. Actually, repeated minor infarcts, or at least sublethal emboli, may precede, for several days and rarely for several weeks, a fatal episode.

MORBIDITY AND MORTALITY

Davis⁵ studied the records of the Massachusetts General Hospital from 1911 to 1925, and found that fatal pulmonary embolus occurred in three patients out of each 1000 subjected to operation. Miller and Rogers⁶ found, in the same institution, that seven patients died of embolus out of 206 with clinical thrombophlebitis. Welch and Faxon,⁷ in a later study, found the ratio of deaths to phlebitis to be about the same (1 to 25). They also found that one patient in three, with phlebitis, would have an infarct. Actually, the rate of fatal embolism has been reduced to one in each 800 operations performed in this institution. This reduction was brought about by a better understanding of venous stasis. Patients were encouraged, and actually aided, in frequent body exercises, deep breathing, and the leg veins kept empty by elevation of the foot of the bed. In spite of these safeguards, there continued to occur sudden deaths from massive embolus, many disabling infarcts, and much concern regarding the outcome in patients who developed thrombophlebitis. *The morbidity in this group of cases was great.* Many of the staff felt that a minimum of six weeks absolute bed-rest was imperative. It was found by Miller and Rogers that fatal embolus had not occurred in this group after the 27th day of the disease. One could never be sure when the process would involve the second leg, thus prolonging the hospital stay. Not only was this a painful, perilous period for all concerned but the patient often developed a permanent swelling in the affected leg, frequently resulting in postphlebitic ulcer.

Many attempts were made to improve the situation. Among these were the use of thyroid extract, heparin, leeches, and lumbar sympathetic block. Thyroid extract was given to the postoperative patients on one of the two

surgical services for a year, and at the end of this period no difference in the two groups was apparent. Leeches were difficult to manage but in a few instances of careful treatment of established thrombophlebitis by this method, the results were not spectacular. Heparin, with all its attended difficulties and cost, was amazing in its action when used according to the dictates of Murray.⁸ Patients with thrombophlebitis on heparin would rapidly become afebrile and their legs symptomless. Since the action of this substance was not supposed to dissolve the original thrombus but prevent propagating thrombi, it was not surprising that difficulties concerning its use arose. Phlebitis would remanifest itself either in the original leg or its fellow after discontinuance of the drug. Infarcts took place after prolonged use of heparin, when it was stopped, and in one instance a fatal embolus occurred. We believe that heparin has its uses but need no longer be considered necessary in all cases. It is particularly helpful as a preventive measure in patients with a previous history of phlebitis, in patients who continue to have small infarcts after vein interruption, and as a preliminary to dicumarol administration. It may well be more effective in the treatment of bland thrombosis than in true thrombophlebitis. We are of the opinion however that simpler and safer methods are available.

Lumbar sympathetic block, first advocated by Leriche and Kunlin,⁹ and popularized by Ochsner and DeBakey,¹⁰ is a very useful procedure. The patient is more comfortable within a few minutes and morbidity is decreased. It is necessary to repeat the block with such frequency that many of our patients object strenuously to the necessary needle punctures of the lumbar region. We have come to look upon it as a valuable preliminary to more radical measures and use it occasionally in this manner. We feel that, as a therapeutic measure in the type of thrombophlebitis which we see, it is associated with too many disadvantages to warrant its complete adoption.

We have had too little experience with dicumarol to warrant any expression of opinion regarding it at this time. The drug has great possibilities in the prevention of thrombosis in suitable cases. Further safeguards are necessary before its use can be widely adopted.

Homans¹¹ is responsible for bringing to our attention the feasibility of interrupting the deep veins of the leg to prevent pulmonary infarction. Frund,¹² Bancroft, Stanley-Brown and Chargaft,¹³ Taylor,¹⁴ and Kulenkampf,¹⁵ have all contributed articles of value to this phase of the subject. Welch, Faxon, and McGahey,¹⁶ and Allen,¹⁷ have published some of the experiences with this procedure from the Massachusetts General Hospital, and it is our intention in this report to analyse the material, up to January 1, 1943, from this institution.

There has been considerable pressure brought upon us by other departments in the hospital particularly by our medical colleagues. They feel that it is not possible to determine the source of infarct and that, since femoral vein interruption has been associated with no serious sequelae, we should undertake this procedure without hesitation. We have complied with this

request because the operation is simple and disturbs even seriously ill patients very little, and because we have found femoral and iliac vein thromboses in many of the cardiac patients who have had infarcts. We hoped that our analysis would make it possible to eliminate some of the obviously unnecessary interruptions and that we might set-up more clearly defined indications for the procedure.

Between 1937 and January 1, 1943, we have interrupted the femoral vein or veins in 202 patients. Bilateral operations, either at the same time or at subsequent dates, bring the total deep veins interrupted to 280 (Table I). The tremendous increase from 55 interruptions in 1941 to 211 in 1942 is due to increased confidence in the procedure and to an increase in the number of bilateral operations.

TABLE I
NUMBER OF FEMORAL VEIN INTERRUPTIONS IN 202 PATIENTS
Massachusetts General Hospital
(According to Year)

1937	1
1938	0
1939	8
1940	5
1941	55
1942	211
Total	280

The sex ratio is surprising, in that we find that 126, or 62 per cent, of the patients operated upon are males. We had expected that, inasmuch as thrombophlebitis was more common in the female, bland thromboses would also prove more common in this sex. In this institution the sex ratio of patients is almost equal.

TABLE II
AGE OF PATIENTS IN DECADES
202 CASES OF THROMBO-EMBOLIC DISEASE
Massachusetts General Hospital—1937-1942 (Incl)

0-10	1	0.5%	19%
10-20	4	2%	
20-30	9	4%	
30-40	24	12%	
40-50	37	18%	81%
50-60	53	26%	
60-70	49	24%	
70-80	25	13%	
Total	202		

The age distribution is important (Table II). We knew that fatal embolus was rare in the young patient and that the danger of this complication was in a direct ratio to the patient's age, from a study of this phase of the subject made in our clinic by Welch and Faxon.⁷ We are, therefore not surprised to find that 81 per cent of the patients receiving femoral vein interruption were over forty years of age. One may well ask why the operation was undertaken in the younger age-group at all. The reasoning

is logical, since the operation is simple, it protects the patient from the added morbidity of pulmonary infarcts and the prolonged hospital stay from the venous thrombosis and also eliminates the chance of a rare fatal embolus

TABLE III

ANALYSIS OF 202 CASES THROMBOEMBOLIC DISEASE TREATED BY FEMORAL VEIN INTERRUPTION

Massachusetts General Hospital—1937-1942 (Incl)

Number of veins interrupted			
Right common femoral	27		20%
Right superficial femoral	10		50%
Total (right)		150	46%
Left common femoral	39		25%
Left superficial femoral	111		75%
Total (left)		150	54%
Total		280	
Number of unilateral operations	124		61%
Number of Bilateral operations	78		39%

An analysis of the veins interrupted is shown in Table III. We had supposed that there would be a greater number of left veins operated upon since there has been some statistical data on an anatomic basis to support a greater frequency of thrombophlebitis in the left leg veins. Our tendency to increase the number of bilateral ligations may have influenced these figures. The location of interruption above or below the profunda femoris vein may be of little importance, although we have contented ourselves with the superficial femoral vein in from 75 to 80 per cent of the cases. We thought this procedure would result in a shorter period of postoperative edema, and, occasionally, even in the presence of profunda femoris thrombosis, we have not always interrupted the common femoral. Actually, when one removes the thrombus by suction from the iliacs, it may make little difference where the vein is ligated and divided, usually, however, if the profunda is thrombosed, the interruption has been above it. It is quite likely that some of the rare infarcts, that occurred after superficial femoral interruption may well have come from the profunda vessels.

TABLE IV

INDICATIONS OF VENOUS THROMBOSIS

No of cases with chest pain as first symptom	82	41%
No of cases with leg signs as first symptom	120	59%
No of cases with suitable charts for study	74	
No of cases with positive clinical chart noted	60	81%
No of extremities examined for swelling	237	
No of extremities showing swelling	159	67%
No of extremities examined for tenderness	231	
No of extremities showing tenderness	143	61%
No of extremities examined for Homans sign*	139	
No of extremities showing positive Homans sign	59	42%

*Homans sign is a term used in our clinic. Dr. John Homans calls it the dorsiflexion sign. It is carried out by dorsiflexion of the foot with the knee straight. If the patient complains of pain or soreness in the calf muscles when this is done the sign is interpreted as positive for venous thrombosis.

Indications for femoral vein interruption are shown in Table IV. Fifty-nine per cent of the cases had leg signs or symptoms as the first indication of trouble, while 41 per cent had chest pain first. This undoubtedly explains the fact that there has been an occasional fatal embolus during an otherwise apparently normal convalescence, in spite of our alertness regarding bland thrombosis. When the clinical chart shows an elevation of temperature, pulse, and respiration, one should examine the patient's legs with utmost care and if minimal signs are noted, proceed with bilateral femoral vein interruption. We regret to say that, due to the difficulty in maintaining a four-hourly chart, many of these early warnings are missed. Also, we believe it is important to have an elevation of temperature, pulse, and respiration together, since one or two of them may be elevated while the second or third, or both, may be unchanged.

Phlebography appeared to be the solution to the question of a reliable indication for vein interruption. Welch, Faxon, and McGahey¹⁶ became expert in the technic and interpretation of the films and felt, at the time of their publication, that it was a reliable and desirable method of procedure.

TABLE V
PHLEBOGRAMS

Positive with positive clinical findings	55	67%
Negative with positive clinical findings	27	33%
Total	82	
Positive with negative clinical findings	19	41%
Negative with negative clinical findings	27	59%
Total	46	
Positive with pulmonary emboli	33	49.3%
Negative with pulmonary emboli	34	50.7%
Total	67	
Positive phlebograms	78	54%
Negative phlebograms	67	46%
Total	145	
No femoral veins interrupted—1941	53	
No phlebograms—1941	36	68%
No femoral veins interrupted—1942	211	
No phlebograms—1942	104	50%

Table V shows the exact experience we have had with phlebograms. There is a definite trend to rely upon this test less as time goes on. The finding of positive clinical evidence of thrombi with negative phlebograms in one-third of the cases makes us feel that only in very doubtful or borderline cases is phlebography indicated. Furthermore, the ideal time to interrupt the femoral vein is when the venous thrombosis is still localized to the lower leg, and it is in these cases that phlebography is most difficult to interpret. We have come to depend on the clinical examination and believe that phlebography will be used less during the present year than in the past in our clinic.

The reliability of our decision for venous interruptions in the 202 patients operated upon are indicated in Table VI. In patients with infarcts 35.7 per

TABLE VI
202 PATIENTS WITH FEMORAL VEIN INTERRUPTION

	Thrombi Found at Operation	Thrombi Not Found at Operation	
Patients with infarcts	30	54	35.7%
Patients without infarcts	56	62	47.4%

cent still had thrombi in the veins, while in those operated upon before infarct occurred, 47.4 per cent had thrombi. This we believe is significant and shows probably that the diagnosis of thrombosis should be followed by venous interruption before infarct takes place if possible. The negative explorations mean that the thrombus, or a portion of it has either left the vein or is still in the lower veins of the leg.

During 1942, many vein interruptions were undertaken upon patients with symptoms localized to the lower leg, and in this group thrombosis of the femoral vein is not expected. Our present opinion is that if possible, the operation should be carried out before thrombosis has extended into the femoral and iliac veins. As our diagnostic acumen improves in detecting early thrombosis, the number of negative explorations will increase yet the protection afforded by the operation is not diminished.

TABLE VII
MORBIDITY STATISTICS IN CASES OF THROMBOEMBOLIC DISEASE TREATED BY VEIN INTERRUPTION
Massachusetts General Hospital—1937-1942 (Incl.)

I Days after vein interruption to flat chart			
No. of cases			162
Average no. of days			4.5
II Days after ligations to discharge from hospital			
No. of cases			84
Minimum no. of days			3
Maximum no. of days			13
Average no. of days			8.4

Table VII gives an idea of the morbidity following femoral vein interruption. It is to be noted that only 162 cases were available for the study of the clinical chart, while only 84 patients could be evaluated on the basis of hospital stay. These are not selected however, and we believe represent a true picture of the situation. Obviously, it was not fair to include in these data, the records of patients remaining in the hospital for heart disease or for the treatment of fractures or complicated surgical procedures nor was it reasonable to include the clinical charts that were affected by the patients' primary lesion. We wish to confirm by these data only the impression that we have acquired a rapid return to health after femoral vein interruption, and an early discharge from the hospital. When one compares these figures with those available for any other method of treatment used for thrombophlebitis, it is evident that the morbidity is tremendously reduced by venous interruption.

Table VIII brings out some interesting data. The majority of the infarcts occur in the lower lobes of the lungs, and the left lower lobe is more frequently involved than the right.¹⁹ This is thought to be due to the

TABLE VIII
LOCATION OF PULMONARY EMBOLI

Left lower lobe	66	69.5%
Right lower lobe	41	36.9%
Left upper lobe	3	2.7%
Right middle lobe	0	0
Right upper lobe	1	0.9%

anatomic arrangement of the pulmonary circulation, and the fact that the blood flow is more rapid through the lower than the upper lobes. An embolus, for this reason, will be carried by the swiftest current to lodge most frequently in the left and right lower lobes. The rarity of embolism of the upper lobes may be of value in ruling out pulmonary embolism when a questionable lesion is found in that part of the chest.

There were, as we expected, a few infarcts after femoral vein interruption. Eleven of the 202 patients had this complication. Two of these patients died after leaving the hospital. One in Case 7 in the analysis of deaths, and may well have had a fatal embolus from the uninterrupted vein on the opposite side. He was a cardiac, and could well have succumbed to heart disease. The other patient died suddenly at home, one month after discharge from the hospital. She had had bilateral superficial femoral interruption, and no thrombi were found at this level. At autopsy, some thromboses were found in the pelvic veins but the fatal embolus was found to have arisen in the right auricle. The other nine patients in this group recovered, four of them were cardiacs. One patient, who had infarcts after prostatectomy, continued to have emboli following bilateral superficial femoral interruption for positive leg signs. He was given heparin for eight days and recovered. Eight of these 11 patients had bilateral interruption. In retrospect, it seems probable that the convalescence could have been shortened in the two survivors who had unilateral operations.

TABLE IX
CARDIAC PATIENTS WHO HAD FEMORAL VEIN INTERRUPTION*

Positive leg signs with clots	4
Positive leg signs without clots	10
Negative leg signs without clots	5
Positive phlebograms with clots	1
Negative phlebograms without clots	8

*All in this group had infarcts or definite signs of phlebitis. Infarcts were doubtless cardiac in origin in some instances.

In the cardiac group (Table IX), we find that in five patients with negative leg signs, no thrombi were found in the veins at operation. On the other hand in ten patients with positive leg signs and in eight with positive phlebograms, no thrombi were found in the femoral veins. One immediately wonders if the absence of thrombi at this level could be interpreted on the basis of thrombi in the veins above this region. In most instances, however, in this group, femoral vein interruption was undertaken on minimal evidence of thrombosis involving the veins of the lower leg, so that it was not expected to find thrombi in the femoral vein. The fact that the femoral vein is opened and free bleeding obtained from both direc-

tions is, in our opinion, evidence that any thrombosis that exists would of necessity be in the smaller veins of the pelvis or of insufficient size to interfere with blood flow through the main veins. We are willing to accept the more likelihood of infarct from cardiac origin in most of these cases.

Patients who died of their disease and who had been subjected to femoral vein interruption, are analysed in Table X. There are 12 in this group, two of them dying after discharge from the hospital, and are mentioned above. All of these patients, we feel sure, succumbed to causes unrelated to femoral vein interruption. Perhaps, one patient died from embolus originating in the uninterrupted vein in the opposite leg. It is surprising to us that such an outcome has not occurred in others in our group. We have, in nearly every instance, interrupted the vein on all legs that have given us positive clues of involvement. As a matter of fact, we have found thrombosis in so many supposedly normal extremities that we are inclined to feel that simultaneous routine interruption of the opposite vein should be undertaken.

SEQUELAE

Sequelae following femoral vein interruption have been surprisingly few. Actually, postoperative edema is the most serious of these and there has been so little complaint on the part of the patients regarding this that it is relatively unimportant. In Table XI, we have tried to bring this out. We were particularly interested in determining, if possible, the difference in edema in superficial and common femoral interruption. It appears that early swelling is more frequent after common femoral interruption but late edema seems to be about the same in both groups. The average patient wears a woven bandage for three to four weeks after discharge and then abandons it as unnecessary. A few are more comfortable with supports for long periods of time. There seems to be less swelling in these extremities than one usually sees following a spontaneous recovery from thrombophlebitis. So far, we have observed only one transient ulcer of the postphlebotic type in this group.

Homans feels that there will be less subsequent edema if the common iliac is divided rather than the femoral. He has anatomic evidence to support this view on the basis of a greater number of contributory veins coming in between the levels of the femoral and iliac veins.

In old cases of thrombophlebitis with infarct, one may do well to interrupt the venous circulation at a higher level. It is usually impossible to remove these old, inflammatory adherent thrombi through an incision in the femoral vein. Doubtless, it is better to interrupt the vein above the thrombus if it cannot be removed. Homans² prefers to ligate the common iliacs through a long oblique ureteral incision retroperitoneally—the right common iliac vein is quite easily exposed by this route. The left vein lying behind and to the right of the artery is more difficult to approach. He has reported six right and six left iliac vein interruptions.

The feasibility of interruption of the vena cava in continuity through

THROMBOSIS AND EMBOLISM

TABLE X
ANALYSIS OF DEATHS

TABLE X ANALYSIS OF DEATHS															EMBOUSIS AND EMBOLISM									
Case	W C	Age	Sex	Diagnosis	Operation	Veins*		Pulmonary Emboli		Clot Found	Days of Disease		Condition of Veins		Cause of Death	Days from Lig of Vein to Death								
						Interrupted	L S F	Before Oper	After Oper		Clot Below Lig	Clot Above Lig	Old	New										
1	W C	65	M	Glaucoma art scl heart dis	Eye operation	L S F	0	+	0	0	0	21	+	+	0	0								
2	M P	66	M	Ca of stomach	Subtotal gastrectomy	L S F	0	0	0	0	0	1	0	+	0	0								
3	A M	62	M	Ca of colon	Resection of colon	R S F	0	0	0	0	0	1	0	+	0	0								
4	J G	45	M	Ca of bladder	Uret-terostomy	L S F	0	+	0	0	0	1	0	+	0	0								
5	A C	62	M	Ca colon	Right colectomy	R S F	0	+	0	0	0	2	+	+	0	0								
6	T L	52	M	Acute cholecystitis	None	L S F	0	+	0	0	0	1	0	+	0	0								
7	R S	39	M	Coronary heart dis	None	R S F	0	+	0	0	0	2	+	+	0	0								
8	M B S	69	F	Coronary heart dis	None	L S F	0	+	0	0	0	1	0	+	0	0								
9	H H	79	M	Sprained ankle	None	L S F	0	+	0	0	0	1	0	+	0	0								
10	B E	39	F	Ca of uterus	None	R S F	0	+	0	0	0	2	+	+	0	0								
11	G G R	52	M	Dermatomyositis	None	L S F	0	+	0	0	0	1	0	+	0	0								
12	C S	40	F	Rheumatic heart dis	None	R S F	0	+	0	0	0	1	0	+	0	0								
						L S F	0	+	0	0	0	1	0	+	0	0								
						R C F	0	+	0	0	0	1	0	+	0	0								
						L C F	0	+	0	0	0	1	0	+	0	0								
						R C F	0	+	0	0	0	1	0	+	0	0								
						L C F	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
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						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
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						R S F	0	+	0	0	0	1	0	+	0	0								
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						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
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						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
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						L C I	0	+	0	0	0	1	0	+	0	0								
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						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
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						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0	0								
						R S F	0	+	0	0	0	1	0	+	0	0								
						L C I	0	+	0	0	0	1	0	+	0									

a right loin incision, similar to that used in lumbar sympathectomy, has been demonstrated by one of us¹⁸ This is certainly the procedure of choice if bilateral iliac interruption was indicated

The total salvage from femoral vein interruption is enormous Although it may not be possible to prevent all deaths from massive bland thrombi, the possibility must be kept constantly in mind, so that minor signs and symptoms will not escape our attention On the other hand, the morbidity saving is unquestionable and tremendous One may decide to attempt preventive vein interruptions in certain predisposed, or elderly individuals This seems to us difficult at the moment, since prediction regarding such complications is unreliable in the light of our present knowledge

TABLE VI
POSTOPERATIVE EDEMA FOLLOWING FEMORAL VEIN INTERRUPTION
Massachusetts General Hospital—1937-1942 (Incl)
IMMEDIATE EDEMA

	Number of Cases	Number With		Number Without	
Right common femoral	19	13	70%	6	30%
Left common femoral	34	29	85%	5	15%
Total	53	42	80%	11	20%
Right superficial femoral	78	37	47%	41	53%
Left superficial femoral	82	39	48%	43	52%
Total	160	76	47.5%	84	52.5%
LATE EDEMA					
Right common femoral	6	2	33%	4	67%
Left common femoral	20	10	50%	10	50%
Total	26	12	46%	14	54%
Right superficial femoral	26	8	31%	18	69%
Left superficial femoral	31	16	52%	15	48%
Totals	57	24	42%	33	58%

OPERATIVE TECHNIC

The operation of femoral vein interruption as carried out in our clinic is as follows The patient is operated upon with a slight elevation of the trunk to insure positive venous pressure from above Novocain infiltration anesthesia is used The incision is guided by the pulsation of the femoral artery in the groin and extends distally three inches in the direction of the vein We believe this allows a better retraction of the lymphatics and a minimal division of them—this offsets the advantage of an oblique incision making for a fine scar The femoral sheath of the vascular bundle is divided longitudinally and the artery retracted laterally The vein is exposed over a distance of two inches in the center of the vertical skin incision This brings into view the common, superficial, and deep femoral veins, which are freed sufficiently to allow a ligature to be placed under them These ligatures are left untied and used to control bleeding after the vein is incised If the common femoral appears thrombosed, it is opened, if it appears uninvolved, the superficial femoral is opened The incision

in the vein is made transversely and through only the anterior half. Thrombi extrude through the incision and are withdrawn from the upper segment first. Suction, carefully applied, through an angulated glass drinking tube, which is inserted through the vein incision into the iliac, frequently makes it possible to clear the proximal segments sufficiently to allow free bleeding. After this is accomplished, the lower segment is cleared of thrombus by the same method. The introduction of the aspirating cannula proximally has never dislodged a thrombus. The previously placed ligatures are then tied and the vein completely divided. Transfixion sutures distal to the ligatures are then used. The wound is washed out with salt solution and closed without drainage.

The entire procedure requires about 30 minutes. In the inflammatory veins, the patient feels slight discomfort during the manipulation of the vein. Patients are allowed out of bed as soon as they become afebrile or their general condition permits. This is often on the day following the removal of a bland thrombus. We have rarely been troubled with a short period of lymph drainage through the wound.

SUMMARY AND CONCLUSIONS

1 Femoral vein interruption for the prevention of pulmonary embolism is a simple, safe operative procedure and can be carried out upon very ill patients.

2 The indications are usually apparent. Pulmonary infarcts, tenderness over the leg veins, swelling of the leg—however slight, dilated superficial veins, discomfort in the calf muscles if the foot is passively dorsiflexed (Homans' sign), and slight elevation of the temperature, pulse, and respiration, are all satisfactory guides. One usually has to make a decision on one or two of these criteria, although frequently all are present.

3 Phlebograms are difficult to interpret and may be misleading.

4 In a large majority of cases, bilateral interruption should be undertaken. Unilateral interruption may be safely done as the indications arise in the younger age-group. In patients beyond the age of forty, bilateral interruption at one sitting should be the rule.

5 We are sure that mechanical removal of the thrombus from the vein by aspiration is a safe procedure. It certainly reduces the pain and swelling in the leg, and hastens recovery.

6 No deaths have occurred in a group of 202 patients as a result of femoral vein interruption.

7 Sequelae are not severe and they are not disabling.

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PEROXIDE OINTMENTS¹

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THE VALUE OF PEROXIDE THERAPY has become established in recent years for a variety of surgical conditions. We are indebted principally to Meleney, and his associates,^{1 2 3 4 5 6 7 8 9} for their demonstrations of its capabilities in the treatment of progressive bacterial synergistic gangrene, chronic undermining burrowing ulcers on all parts of the body surface, gas gangrene and tetanus after excision of involved tissues, fusospirochaetal infections of the mouth and neck and human bites infected with these organisms, chronic ulcerations of the vagina, perinectal and deep pelvic abscesses, diabetic infectious gangrene, amebic infection with gangrene, lung abscess, actinomycosis, and other malodorous infections. It has also been described in the treatment of decubital ulcers,¹⁰ foul smelling infected malignant lesions and radionecrotic ulcers by a number of authors^{11, 12, 13}. The effectiveness of zinc peroxide in arresting the continued hemorrhage complicating chronically infected burns after all other forms of therapy that had been tried had failed was reported from this clinic¹⁴ one year ago.

It has also been used postoperatively as a prophylactic dressing for recent accidental wounds^{15, 16} and for wounds resulting from operations for fecal fistulae, pilonidal sinuses and rectal and colonic lesions.

More specifically, peroxides are indicated principally in the case of wounds or other lesions caused, or secondarily infected, by anaerobic streptococci, microaerophilic hemolytic and nonhemolytic streptococci, *Cl. tetani*, anaerobes of the gas gangrene group, *B. melanogenicum*, *B. fusiformis*, *Actinomyces*, and certain Spirochaetes.

In the past, peroxide therapy has been limited largely to the use of hydrogen peroxide irrigations or the daily application of a water suspension or cream of zinc peroxide. The chief disadvantage of hydrogen peroxide is the rapidity with which all of its oxygen is dissipated on a wound surface, necessitating frequent or continuous irrigation by this solution. Although zinc peroxide suspended in water has been found to be very effective therapeutically, it has certain disadvantages which tend to limit its use to large and well-equipped hospitals.

1 The physical activation of the zinc peroxide powder requires its heating for four hours in a carefully regulated dry oven.

2 The suspension must be freshly and correctly made before each dressing since it will not keep, an obvious disadvantage on a busy ward, in the home, or the office.

* Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio

3 Daily dressings are required because the oxygen is usually dissipated in the wound in 24 hours or less

4 Suspensions of zinc peroxide and the oxide and hydroxide which it forms have a tendency to congeal as flakes or concretions which may be difficult to remove without causing pain or bleeding from the depths of a wound. If allowed to remain in the wound for any length of time they may excite a local foreign body reaction

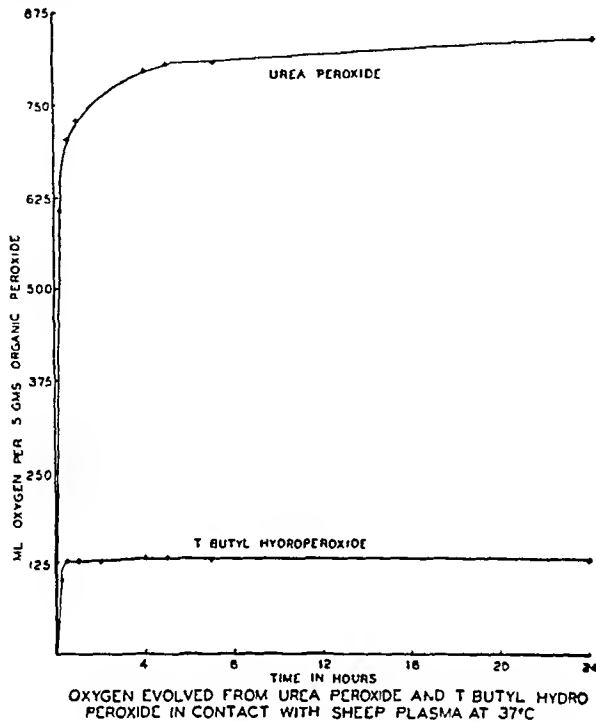


FIG 1

It is our impression that the field of usefulness of peroxide therapy would be definitely extended if one or more active and stable peroxide ointments were generally available. Until the present most attempts to produce an active and stable ointment have failed principally because of the lack of a suitable ointment base. In our experience as well as in that of Meleney,¹⁷ the ordinary grease ointment bases greatly decrease the activity of zinc peroxide, while greaseless bases or vanishing creams containing zinc peroxide permit satisfactory evolution of oxygen if used immediately, but do not make stable ointments.

During the past one and one-half years, we have studied the problem of producing an active and stable peroxide ointment in association with the Research Division of the William S Merrell Company. Our first efforts were directed toward the development of a suitable base. A satisfactory base had to be water-soluble yet contain or absorb no water on standing. It had to have a melting point at body temperature, so that its application would be followed by the filling of all the recesses and depths of the wound insuring intimate and continued contact with these surfaces. Such a base

was found in the solution of "Carbowax"-1540 by one of several glycol diluents such as hexaethylene glycol-polyethylene glycol-300 or nonethylene glycol-polyethylene glycol-400. The proportions of these constituents used can be varied according to the amount and type of peroxide to be used. The "Carbowax" and the glycols are produced by the carbide and Carbon Chemicals Corporation of New York City. "Carbowax"-glycol ointment base used on experimental and human wounds is nontoxic and does not appear to alter perceptibly the rate of wound healing.

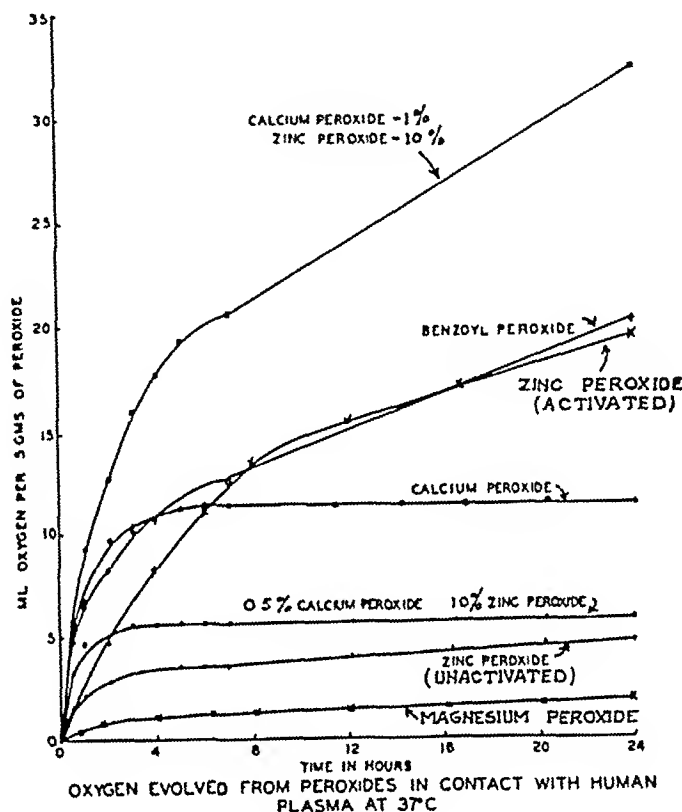


FIG. 2

Using the "Carbowax"-glycol base it is possible to make a suitable ointment with zinc peroxide. It is significant that Meleney, working independently and at about the same time, also decided upon "Carbowax" as the most satisfactory ointment base for zinc peroxide. After considerable experimentation with different combinations of "Carbowax" and the various glycols, a satisfactory zinc peroxide ointment was developed having the following formula:

"Carbowax"-1540	120 Gm
Nonethylene glycol-polyethylene glycol-400	80 cc

These are mixed thoroughly in a boiling water bath until dissolved. To the cooling solution is added 10 per cent finely milled, activated zinc peroxide and 0.2 per cent of cetyl pyridinium chloride which are stirred continually until a smooth homogeneous ointment is formed.

Other glycols such as hexaethylene glycol-polyethylene glycol-300 can be used satisfactorily with the "Carbowax" by varying the proportions. Merck's or Mallinckrodt's medicinal grade of zinc peroxide should be used,

and activated by heating to 140°C for four hours in a dry oven for best results, although a less effective ointment can be prepared from the unactivated material. Cetyl pyridinium chloride is a wetting agent as well as an effective antiseptic, and the addition of 0.2 per cent of this substance increases the amount of oxygen released by zinc peroxide by approximately 20-25 per cent. This ointment is yellowish-white in color, moderately greasy in consistency, has a melting point of $38-39^{\circ}\text{C}$, and a p_{H} of 7.2. If lanolin is added to the above formula, the evolution of oxygen from the zinc peroxide is decreased 27 per cent.

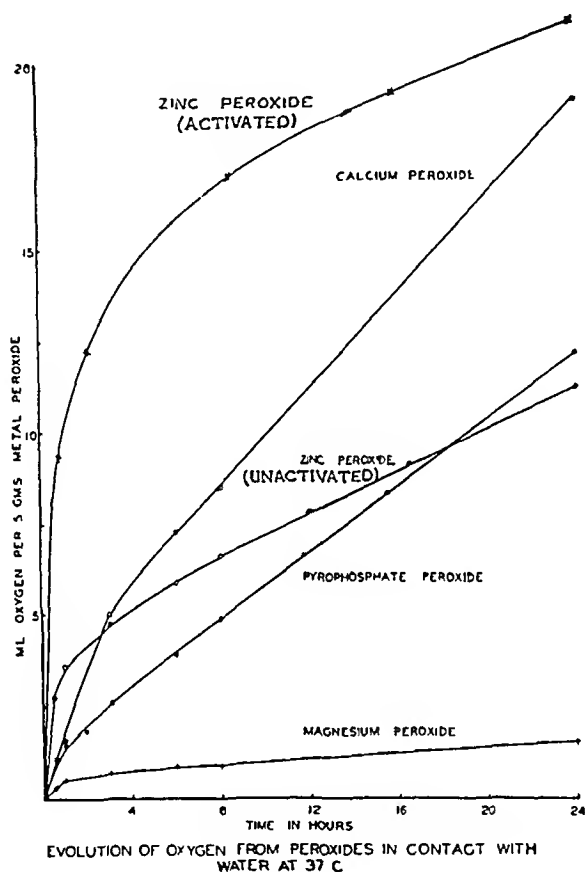


FIG 3

This ointment will release oxygen when coming in contact with water, serum, plasma, perspiration, or wound secretion. This is important, in that oxygen will be evolved from zinc peroxide in an open wound or lesion without the addition of water, the reaction apparently being dependent upon peroxidase present in the secretions. The greater the effusion of wound juices, the greater the release of oxygen over a 24-hour period and, under some conditions, a three- to four-day period (Fig 1). During its decomposition in water this ointment has a p_{H} of 9.55, and in plasma a p_{H} of 9.4.

To test the stability of this ointment, samples were stored at 37°C for six months (high above the average room temperature). Under such conditions the ointment held up well, and the total amount of oxygen evolved

from a five Gm sample of ointment decreased only 6.5 per cent after two months and only 15.2 per cent after six months. The rate of oxygen released after this period of storage follows the same general curve as that of the freshly prepared ointment. It is to be remembered that the decomposition of zinc peroxide powder is much more rapid during the first month after its activation.

Our clinical tests with this ointment over the past eight months have been satisfactory. The technic employed in dressing a granulating wound, or other lesion, consists of preliminary gentle cleansing of the surface with

OXYGEN EVOLVED FROM
ZINC PEROXIDE OINTMENT

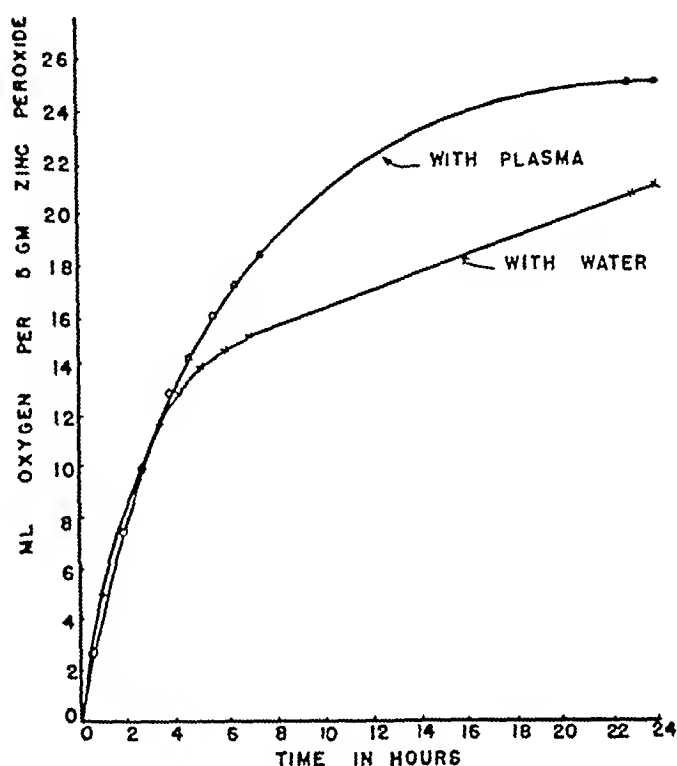


Fig 4

hydrogen peroxide and saline solution, followed by the liberal application of the ointment to insure complete, intimate and lasting contact with all parts of the lesion. The low melting point of the base facilitates this. Since the zinc peroxide is gradually decomposed by wound secretions or plasma, it is not necessary to add water, or to cover the ointment with gauze or cotton pads soaked in water, although we have usually done this. A layer of vaseline or zinc oxide ointment gauze is then used to cover the area and seal in the evolved oxygen and the wound secretions. The interval between dressings may be 24 to 72 hours, but our experience indicates that it should never be as long as five or more days because of the reaction the residue, namely, zinc oxide and zinc hydroxide, may produce in the wound. In such cases a marked increase in the amount of purulent exudate may occur and this exudate may also become bloody. We have thought that this was the result of a foreign body reaction produced by the zinc oxide and zinc hydroxide residue.

If the proportion of "Carbowax" is increased and that of the glycol is decreased, a satisfactory base is obtained for making zinc peroxide vaginal or rectal suppositories.

Other peroxides have been studied to see if any was superior to zinc peroxide for peroxide therapy. Two main groups of peroxides were available for this purpose, the inorganic and the organic. The inorganic group contained metallic radicals and consisted of zinc peroxide, calcium peroxide, sodium pyrophosphate peroxide and magnesium peroxide. The organic group consisted of urea peroxide, benzoyl peroxide, benzyl peroxide and tertiary butyl peroxide.

APPARATUS AND PROCEDURE FOR STUDYING THE EVOLUTION OF OXYGEN FROM PEROXIDES

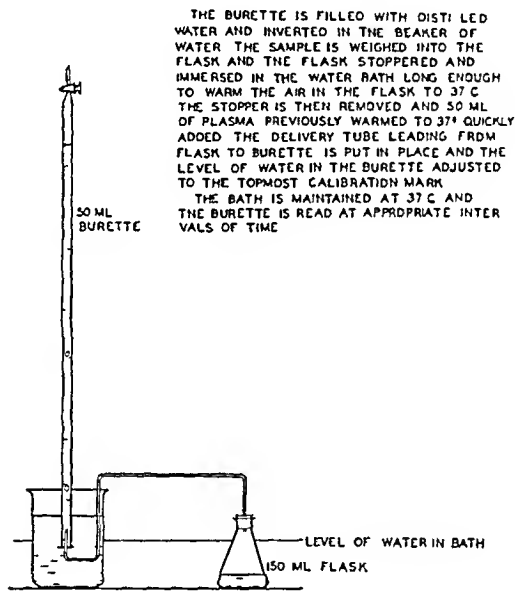


Fig 5

The inorganic peroxides are insoluble in water but are decomposed gradually at a sustained rate by water, blood, plasma, and wound secretions, giving off comparatively small quantities of oxygen and leaving a residue. The organic peroxides tend to be soluble in water and are decomposed rapidly by plasma, leaving no insoluble residue. Water, however, causes very little release of oxygen.

To study the evolution of oxygen from the various peroxides, a simple but effective apparatus was devised by the Merrell Research Laboratories, which is depicted and described in Figure 2. The rate and amount of oxygen released by the inorganic peroxides in the presence of water at 37°C was measured and is illustrated graphically in Figure 3. Zinc peroxide after preliminary activation by heat produces the greatest amount of oxygen at a sustained rate. If unactivated, the amount of oxygen released is reduced 60 per cent. The curve produced by calcium peroxide is very satisfactory while those by sodium pyrophosphate peroxide and unactivated zinc peroxide are similar.

to each other. The small amount of oxygen released by magnesium peroxide makes it obviously not suited for this purpose.

A comparison of the evolution of oxygen from the various peroxides in the presence of human plasma at 37°C is shown in Figures 4 and 5. The rate and amount of oxygen released by activated zinc peroxide in the presence of plasma is very similar to that released in the presence of water, while magnesium peroxide, unactivated zinc peroxide and calcium peroxide give off very small amounts of oxygen. The curve of benzoyl peroxide is very similar to that of activated zinc peroxide but its highly explosive and inflammable nature precludes its use topically for clinical purposes. Urea peroxide and T-butyl hydroperoxide both release much larger quantities of oxygen than activated zinc peroxide, but the evolution is so rapid that it is complete in four to eight hours, an obvious disadvantage.

Ointments may be prepared with each of the above peroxides using the "Carbowax"-glycol base. The inorganic peroxide ointments can be made stable but the organic tend to be unstable. Urea peroxide ointment if carefully made will remain stable.

The p_H of the various peroxide ointments in the presence of water and plasma is shown in Table I as determined by the Leeds and Northrop glass electrode potentiometer.

TABLE I

	ZnO 10%		CaO 10%		MgO 10%		Urea Peroxide		T Butyl Hydro-Peroxide	
	H ₂ O	Plasma	H ₂ O	Plasma	H ₂ O	Plasma	H ₂ O	Plasma	H ₂ O	Plasma
5 mins	7.2	9.3	12.0	11.0	10.0	9.75	3.30	5.90	4.68	6.5
4 hrs	9.55	9.4	11.24	11.05	9.9	9.86	4.20	5.75	3.9	6.8
24 hrs	9.30	9.74	11.95	11.13	10.06	10.10	3.35	5.66	4.14	6.5

The results are very interesting. It will be noted that the inorganic peroxides produced an alkaline reaction in the presence of either water or plasma, while the organic ones gave strongly acid reactions. The low p_H given by urea peroxide and T-butyl peroxide and the high p_H produced by calcium peroxide indicate the irritant nature of these substances when applied to wounds or other lesions. Plasma has a buffering action which decreases to a certain extent the acidity or alkalinity of these preparations.

Our clinical investigations have been limited to the use of zinc peroxide and urea peroxide ointments. Zinc peroxide ointment has proven satisfactory when used for specific indications, as described by Meleney. We have noticed rapid control of infection and disappearance of foul odors with no apparent delay in wound healing. If the zinc peroxide dressing was not changed at least every two or three days, and the residue was allowed to remain on the surface of a raw or granulating wound for a period of five or more days, a marked increase in bloody purulent exudation occurred, presumably from the irritant action of this foreign body. With three per cent urea peroxide ointment, more frequent change of dressings were necessary since the rate of oxygen evolution was rapid and unsustained. Its

use on infected wounds containing considerable slough was usually followed by rapid control of infection and separation of the necrotic tissue. Although urea peroxide does not leave an insoluble residuc in the wound and although it may have a synergistic effect with sulfanilamide our repeated observations show it has three very serious disadvantages. Its local irritant action, a marked delay in wound healing occurring with its continued use, and its sudden unsustained release of oxygen. The rapid evolution of oxygen produced by urea peroxide ointment makes it an effective prophylactic agent for lewisite burns. Our experiments have shown that application of this ointment to the skin as long as ten minutes after exposure to lewisite vapor or liquid will either entirely prevent or greatly diminish the size and severity of the local lesion.

SUMMARY AND CONCLUSIONS

The value of active and prophylactic peroxide therapy has become established for a variety of surgical conditions. For most effective use peroxide therapy should not be employed indiscriminately but should be used intelligently and be limited to specifically indicated conditions. It is our belief that treatment by Dakin's solution is still the most satisfactory therapy for the majority of infected granulating wounds or lesions seen by the surgeon.

From our studies, it is obvious that the ideal peroxide for local therapeutic use has not been found as yet. Each peroxide investigated has its disadvantages, but of those studied zinc peroxide still seems to be the most effective and satisfactory. Its chief advantages are safety and durability of action.

Certain disadvantages of using water suspension of zinc peroxide tend to limit its use to large and well-equipped hospitals. To overcome many of these disadvantages and to extend the field of usefulness of peroxide therapy, an active, effective, and stable zinc peroxide ointment has been developed.

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DISCUSSION—DR FRANK L MGHAN (New York) Doctors Altmeier and Reid have made an important contribution to the study of surgical infections, as their report clearly indicates. There have been very real difficulties in the clinical use of zinc peroxide powder suspended in water. The chief disadvantage is that it must be kept moist in order to have it remain active in its oxygen evolution and in order to prevent mechanical irritation of the wound if it dries up. This disadvantage may be obviated by covering the innermost dressing (which may be either a thin layer of cotton or fine-mesh gauze) with an outer layer of cotton soaked in water, which is then sealed over with a rubber sheet, if it is a flat surface, or with zinc oxide ointment-impregnated gauze, if it is a curved surface. One great advantage of this dressing is that it can be removed very readily and is never adherent to the wound if it remains moist. If properly sealed it will remain moist for 48 hours. If the zinc peroxide in this dressing is examined after 48 hours it will be found that there is still active zinc peroxide present. In the perineal wound of an abdomino-perineal operation or any deep cavity, it will remain moist and active for a much longer period of time. I have left it in a perineal wound for nine days without having it dry. Heating is advisable to sterilize it and activate it to its maximum efficiency, but the latest preparations are reasonably active without heating and may be used safely in badly infected wounds. The heated preparations do not deteriorate now, as they did formerly, and may be used as long as a year after activation.

We have been looking for a long time, however, for some medium in which the zinc peroxide would be active without drying, and have only recently found such a medium. Quite independently, Doctor Altmeier and I have both come to the use of the glycol preparations known as the "carbowaxes." Great interest in vehicles has recently been stimulated by the necessity for finding a suitable medium for the sulfonamide group of antiseptics, and the "carbowaxes" have been put forward as possibilities in this field. They represent a whole series of glycols varying in molecular weight and running all the way from thin liquids to dense solids. The liquids and solids may be mixed in appropriate proportions in order to give any desired consistency and melting point. The simpler ethylene glycols are toxic but triethylene glycol and the higher glycols are apparently nontoxic, and may be repeatedly injected into animals in large quantities without any harmful effects.

This is still in an experimental stage of development, and the ideal medium will be found, I believe, by further experimentation. Doctor Altmeier's study of the oxygen evolution of these various preparations and the hydrogen ion studies are very important in this development.

I fully agree with Doctor Altmeier that with any surgical infection there must

be a careful analysis of the active organisms and the appropriate treatment must be determined on the basis of this knowledge. Zinc peroxide is not only a bacteriostatic agent but bactericidal for the anerobic and micro-aerophilic organisms as well as for many of the aerobes, particularly the hemolytic streptococcus and other aerobes which are susceptible to peroxides. It also neutralizes, probably by oxidation, many toxins both bacterial and chemical. Among the latter are the poison ivy toxin and the irritating chemicals of mustard gas and lewisite. In addition, in the higher concentrations it is also bacteriostatic for such organisms as staphylococci and pyococcus. For its effective action, there must be close contact and if a wound has a considerable amount of slough this must be largely separated first. Dakin solution is the best means we now have of liquefying the slough. However, there are many limitations to its use which are too well known to mention here. It was hoped that urea could be depended upon to liquefy slough, but it delays wound healing and has other disadvantages.

I want to congratulate Doctor Altemeier on the work he has done in this field, and I hope that others will follow the investigations both in the laboratory and in the clinic.

DR WILLIAM A. ALTEMEIER (Cincinnati, Ohio closing) I wish to emphasize again that we believe zinc peroxide therapy should be limited to specifically indicated lesions and should not be used indiscriminately. We believe, too, that the intelligent use of Dakin's solution is still the most effective form of therapy for the average infected granulating wound seen by the surgeon.

ERRATUM

TRAUMATIC SHOCK. AN EXPERIMENTAL STUDY INCLUDING EVIDENCE AGAINST THE CAPILLARY LEAKAGE HYPOTHESIS. Jacob Finc, M.D., Arnold M. Seligman, M.D., and Howard A. Frank, M.D. ANNALS OF SURGERY, 118, No. 2, 238-255, August, 1943.

The name of Howard A. Frank, M.D. should be deleted as a co-author, and also removed from the running heading.

ADDENDUM

LIVER NECROSIS IN BURNS. F. W. Hartman, M.D., and H. L. Romence, M.D. ANNALS OF SURGERY, 118, No. 3, 402-416, September, 1943.

The original manuscript of this article was received for publication in the ANNALS OF SURGERY, March 17, 1943, having first been submitted to the National Research Council on February 11, 1943. It had been scheduled to appear in the ANNALS OF SURGERY for May, 1943, but had to be deferred to the September issue because of paging limitations. The paper was read before the American Society of Clinical Pathologists, Chicago, June 5, 1943.

EXPERIENCES OF A SURGICAL CONSULTANT OF A SERVICE COMMAND*

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ABOUT A YEAR AGO the Surgeon General of the United States Army established a consultant service for the Service Commands comprised of staff of three medical officers qualified in medicine, surgery and neuropsychiatry. Their duties are to evaluate the professional qualifications of the medical personnel, appraise new therapeutic methods and agents and coordinate professional practice by local discussion with hospital staffs of such problems as may present themselves.

It has seemed of interest to present some facts regarding the scope of the activities of the surgical consultant to a Service Command, to show the manner in which he functions and to discuss briefly some of the problems encountered and show how they are being met.

The various fields of medicine and surgery were assigned by the Surgeon General as follows:

MEDICINE All medical specialties (except neuropsychiatry) venereal disease, dermatology, dietetics and clinical pathology.

SURGERY All surgical specialties (including urology, otorhinolaryngology, radiology and physical therapy).

NEUROPSYCHIATRY Neurology, psychiatry and war neuroses.

The following remarks will be principally confined to the field of surgery.

In order to understand the hospital problem in an army at war one should appreciate first of all the difficulties under which a new installation is set up. In times like the present, a hospital of one or two-thousand beds is created in a cotton field or cow pasture in a few months' time. Thereafter, a heterogeneous group of doctors, dentists, veterinarians, nurses, sanitary and medical administrative corps of officers are sent. With the help of a cadre of enlisted men and of civilian employees the hospital must be placed in operation with the minimum of delay. This conglomerate group must not only learn their individual duties but learn how to function effectively as a unit.

The medical officers come from all sections of the country and have greatly divergent viewpoints and varying degrees of training. It would ordinarily take considerable time to complete this integration, yet time is so essential that the hospital must begin to receive patients before it is fully accomplished, and when patients are received they must be given adequate care immediately. This coordination of the professional services is among the most important of the consultant's duties.

* Read before the American Surgical Association, May 13-14, 1943, Cincinnati, Ohio.

OBJECTIVES OF A SURGICAL CONSULTANT

The objectives of the surgical consultant are varied but they all have but a single purpose—to provide the best possible care of the sick or wounded soldier. All other aims are subordinate.

The policy has been to carry out this objective by having the Consultant make and maintain intimate contact with the services of the medical installations in the Service Command. The aim has been to correlate the various sections with the service as a whole and that of the services with one another, to assure the hospitals as even a distribution of qualified specialists as possible, to encourage and advise the officers in better performance of their duties and to raise as far as possible the standard of professional care by means of postgraduate education. There is a general agreement among us in the Service Command that the standard of professional care is no better than the educational level of its medical officers. We are unanimous in the feeling that the type of graduate education best adapted to our needs is that which is brought to the hospital. This enables us to reach the whole staff, including the younger medical officers who should after all be our chief concern. By contact with distinguished civilian or army doctors they can learn by doing. We shall obtain funds from one of the foundations to carry out such a program which will include such features as

- a* The institution of weekly clinicopathologic conferences
- b* The introduction of clinical case teaching in psychiatry
- c* Encouraging the establishment of bimonthly journal club meetings for the express purpose of reviewing the current medical literature
- d* Weekly meetings of the major services
- e* Monthly staff meetings
- f* Grand ward rounds
- g* Inviting nationally known internists, surgeons, psychiatrists, pathologists and radiologists to visit the larger medical installations for a day or two. The invited guests will make ward rounds, hold clinics, give demonstrations, etc.

ACTIVITIES OF A SURGICAL CONSULTANT

The surgical consultant's sphere in relation to the civilian hospital is clearly understood by all of you. He has attained that position by virtue of his years of experience in his chosen field which was often gained in the hospital he now serves as consultant. He is familiar with its professional and administrative components. In the army, however, his activities necessarily differ considerably. He is not merely called upon to assist in the diagnosis or treatment of a specific case. Indeed, this is a small and relatively unimportant part of his function.

The major duties of a surgical consultant to a Service Command center about his visits to the hospitals. His value lies in his ability to acquire an intimate knowledge of the men on the surgical services and to appreciate

then individual problems. Effort should be made to harmonize the methods of treatment with established Army procedure, yet without destroying initiative or interfering unnecessarily with the independent action of the Chief of the Service and his section chiefs.

He should study methods in use and, by observing the results of trial of experimental procedures, he can evaluate them and pass the information along from one camp to another through the medium of the Service Command or by word of mouth. He is a sort of circuit rider who picks up ideas and methods and distributes them from one to another.

He must assist the personnel officer in every possible way to the end that the spread of surgical officers be as even as possible, that deficiencies of personnel are corrected and that the most efficient use is made of the supply of trained surgeons. There has been some recent criticism by members of teaching institutions of the policies of the Army in selecting men for medical officers. In all probability the magnitude of the task of furnishing competent medical officers not only for all the fixed hospitals but for countless units for overseas service, is not generally appreciated by civilian doctors. Already, many men have been transferred to these units and the staffs of our fixed hospitals have not been receiving comparable replacements. It is foreseen that in the months to come there will be an increasing need for economies of surgical personnel. Already an effort is being made to train an officer as an understudy for each important position on the surgical service. Methods are being explored that will lift some of the administrative burdens that diminish the available time and energy that might otherwise be spent in purely professional activities.

RELATION OF THE SURGEON TO THE TRAINING PROGRAM

The surgeon is concerned with the care of the soldier from the time he arrives, still a civilian, at an induction station until he is discharged from the army. Let us consider the various stages at which our contact with him takes place.

The induction station is not only the first but also perhaps the most important. For here is the first and most effective point at which the physically unfit should be weeded out. It is regrettable that the induction station examination fails to eliminate so many men who are destined later to be separated from the service.

To anyone who has observed men at the induction station and during their training program, it is an unescapable fact that the physical condition of the youth of this country is not what it should be. Colonel Leonard Rowntree has pointed this out in a recent interview with a prominent sports editor. He stated that one out of four of the 17- and 18-year-old group is rejected on physical grounds, while in Sweden the rate is but one in ten. The need for a more intensive effort to provide our boys in school and college with better body building and physical toughening should be more generally appreciated and steps taken on a large scale to improve this situation.

The next, and also very important, place where screening takes place is at the Reception Center. Here, too, the great bulk of selectees who have defects or physical limitations that prevent their being of use to the army are weeded out.

The Replacement Training Center, where the recruit undergoes his basic training, is also a point at which further elimination occurs. This is the first stage at which the ability of the soldier to stand-up against the rigors of training is put to the test. Here the foot disabilities, the knee and back conditions, the overlooked herniae and pilonidal cysts begin to present themselves. Before the basic training has progressed very far the vast majority of defects that are destined to disqualify should have been noted, and the sooner they are discovered the better for the Army and for all concerned.

Considering the physical condition of the average inductee, the training program is certainly strenuous. The long hikes with full pack, the obstacle course and the other measures for toughening the soldier are responsible for bringing to light many latent physical defects and for many accidents.

Upon completion of basic training the soldier is assigned to a tactical unit and from there on he is subject to the injuries and accidents common to the branch to which he is attached. The types of trauma sustained bear a direct relationship to the training program he is undergoing.

From the time a soldier arrives at the Reception Center until he reaches a staging area to be sent overseas, the station hospital bears the brunt of his medical and surgical care.

The camp dispensaries serve as counterpart in the Army of the doctor's office or the outpatient department of a civilian hospital. It is here that the soldier reports for sick call, is examined by the medical officer and if his condition warrants it, is sent directly to the station hospital. The dispensary therefore, fills an essential function. It acts as a dam to hold back the flood of potential admissions to the hospitals which without it would be overwhelmed by a host of patients with minor ailments. The dispensary also makes it possible to keep more men on duty lessens the ineffective rate and thus speeds the training program. A man who can be kept out of the hospital without harm to himself is far better off. The trend is definitely toward treating on a duty status all minor conditions in which hospital care is not actually needed. It is therefore, important for the surgical consultant to visit these dispensaries and to assure himself that they are fulfilling their proper function.

GENERAL HOSPITALS

When the soldier completes his training and is ready for overseas service, he is sent to a staging area and there he passes out of our sphere. However when he returns as a casualty he is sent to a general hospital where his care again becomes our concern. Just as the station hospital provides for all the ordinary professional care, the relief of uncomplicated surgical conditions, so the general hospital serves as a "medical center" in civilian

life Here the professional attainments of the staff are expected to be of the highest, the facilities for diagnosis of obscure conditions of the best, and the opportunity exists for prolonged care of cases that require it

There is a growing scarcity of highly-trained and qualified surgeons for positions of responsibility in the general hospitals As a consequence, in some of these hospitals, the level is somewhat below the desired standard In others, there is a lack of qualified specialists in such fields as neurosurgery, plastic surgery and thoracic surgery The correction of these deficiencies is one of the consultant's chief concerns

SURGICAL CONDITIONS COMMONLY ENCOUNTERED

While examples of almost every conceivable variety of surgical conditions are encountered, the vast majority are of two types

a Conditions commonly seen in young adult males, unrelated to Army service

b Accidents or injuries due to the training program In addition, there are the usual mishaps sustained by the soldier on leave or on pass

Under the first category we see many cases of hernia, appendicitis, varicose veins, hemorrhoids, pilonidal cyst, and such orthopedic conditions as torn or loose semilunar cartilages static foot disabilities, recurrent shoulder dislocations and disturbed function due to old fractures and dislocations

In the second we find many severe sprains, all types of fractures, including ankle and wrist, and a surprising number of fatigue or march fractures of the metatarsal, accidental bullet wounds, and severe head injuries Burns have not been frequent Trauma serious enough to require immediate or subsequent amputation is not uncommon The nature of the injuries and their severity differ according to the type of training that pertains to each camp For example, the skeletal injuries have been severe and a good many have been fatal in camps where antitank and commando training or tank unit training is given In Air Force hospitals the few fractures seen are generally severe

Anticipating the fact that certain diseases and injuries will require surgical treatment in which a high degree of specialization is necessary, the Surgeon General has designated certain general hospitals for this purpose For example, to give the name of one hospital in each category, Brooke General Hospital for neurosurgery, McCloskey General Hospital, an amputation center, Walter Reed General Hospital, maxillofacial and plastic surgery, Letterman General Hospital, ophthalmic surgery and treatment of blinded casualties, and Fitzsimmons General Hospital, chest surgery When casualties from overseas begin to arrive in large numbers the activities of the general hospitals will be greatly accelerated

THE ARMY VIEWPOINT IN SURGICAL DECISIONS

While in most respects the viewpoint of the civilian and the Army

surgeon coincides, there are certain instances in which they must of necessity differ. The aim of the surgeon in civilian practice is to provide care of the patient and his interests are the only ones concerned.

In the Army, however, the principal objective of the surgeon is to increase as far as possible the number of effective man-days. In general, these two aims coincide and yet there are numerous situations that arise in which the needs of the Army make it insistent that the latter take precedence. Thus, when defects are discovered that obviously existed prior to entry into service, the surgeon must decide whether their correction in the Army is justified or whether discharge from service is a better solution. In reaching this decision he must consider whether after the operation the man is likely to make a satisfactory soldier. This demands an appraisal of him as a whole and may require the assistance of a neuropsychiatric consultation. Then, too, the gravity of the operation, the risk of complications or sequelae, and the probable end-result must be weighed in each individual case. It is here that the medical officer fresh from civilian practice is at a disadvantage at first and must learn by experience how to evaluate these factors to the ultimate advantage of the Army.

Operative procedures that require prolonged dressings or extended convalescence, such as the open packing method of handling cases of pilonidal cysts are not acceptable in the Army because in most camps a man must be on "full duty" or in hospital, there is no such thing as 'light duty'. During the first nine months of 1942, this Service Command had 780 admissions of pilonidal cyst cases to its hospitals. They were responsible for more than 29,000 man-days lost to the training program.

These considerations only apply to elective surgery for conditions existing prior to induction. Where a man develops a disease or sustains an injury while in service and it is clear that it is not related to a preexisting defect, the same general considerations obtain as in civil life and no form of surgical treatment is withheld that promises the most complete cure or restoration of maximal function.

SURGICAL TECHNIC IN ARMY HOSPITALS

The surgeons and specialists attached to the surgical service of station and general hospitals are men who have, until recently, been engaged in civilian practice. Their technic, therefore, is about what one would expect to find in any first-class civilian hospital, the variations in technic reflect the differences to which their previous training has accustomed them.

There is a general regard for the observance of measures to maintain sterility in the operating room. Preparation of the hands, careful masking of all operating personnel, skin preparation, and exclusion of skin by prompt application of towels to the wound edges, are all matters that are given proper consideration. Care and gentleness in handling tissues, avoidance of blunt dissection and rough retraction and general pattering while operating are all given attention. While the use of nonabsorbable ligature and suture ma-

terials is much more widespread than was anticipated, there are still many surgeons who adhere to chromic catgut. There is, however, a noticeable tendency to use it in finer caliber and to insist on meticulous hemostasis and to avoid placing sutures under tension. This is, of course, very gratifying, for it undoubtedly reflects a growing appreciation of the advantages that accrue when so-called "silk technic" with all its implications is adopted. Alloy steel wire is used by a few surgeons who appear well satisfied with results obtained.

The local use of sulfonamides in wounds made by the surgeon varies greatly in the different hospitals. It is probable that it is used more frequently than is strictly indicated and that its daily use on granulating areas that are not grossly infected is unwarranted and may have a tendency to retard wound healing. In this connection, there is also an inclination to give sulfonamide drugs internally in cases of mild superficial infection, without waiting to see the effect of local measures, such as heat and wet dressings, elevation and physiologic rest of the part. Before the advent of these drugs such treatment was generally promptly effective. There is evidence in recent medical literature that in a considerable percentage of cases reactions follow the use of sulfa drugs in patients who have previously been given them. It seems advisable therefore not to use them in mild infectious processes until the beneficial effect of other measures has been tried.

SUMMARY

The activities of a surgical consultant to a Service Command and some of the problems encountered and observations made have been briefly presented.

The quality of the inductees has been disappointing both as to their specific musculoskeletal defects and their general physical development and stamina. The need is apparent for a more adequate nation-wide program to correct this situation and provide more robust and tougher youths.

Surgical technic and the general care of surgical patients are found, for the most part, to be of a high order. Whether or not the expected depletion of the supply of well-qualified surgeons results in a lowering of the standard now existing depends on how successfully we compensate for it by increasing the effectiveness of the surgeons we have.

In closing, let me assure you that the surgical profession need have no fear that the men who are carrying the load in our Army hospitals will fall short of previous high tradition. They are giving conscientious service; their judgment and technic are excellent, and their hearts are in this job.

DISCUSSION—COLONEL GROVER C. PENBERTH. Colonel Coley has covered the subject very completely in his brief presentation. The contribution of the War Department, through the efforts of the Surgeon General, in establishing this consultant service is to be commended. The consultation service, as it applies to the care of the soldier, is helping indirectly to reduce the period of morbidity, the hospital days, and disposing of the individual soldier that will not become a good soldier.

In going about and visiting the hospitals, I am impressed, as Colonel Coley has

emphasized, with the high caliber of young officers that are leading the way in the teaching program as well as the technical work in the hospitals. These young men who have had good internships and others who have had a residency, are leading the way and doing a very constructive job.

In regard to the training program. This will vary in some of the hospitals, but with the individual officer who has been associated with a teaching institution, the postgraduate program of teaching is excellent. Each officer is expected to contribute. In the ward walks, the clinical pathologic conferences and the various meetings of the journal clubs that I have attended, I am impressed with the sincere desire of the officers to acquaint themselves with the Army method of treatment and the proper disposition of patients.

Relative to the responsibility of the consultant in reference to the training and the selection of qualified officers, we try to evaluate each officer from the standpoint of his interest in a particular subject. The Surgeon General in establishing courses that are carried on in civilian institutions certainly has added to the interest and morale of the young men. They are desirous of attending these courses, and I, for one, appreciate the interest that the civilian physicians and surgeons are taking in the officers that have been assigned.

Unfortunately, we can not always assign the officers that make application, but if the courses are to be continued, and I understand that they are, in due time we may have an opportunity of recommending some who may still be on duty in the United States.

In closing, I want to congratulate Colonel Coley on his approach to this responsibility entrusted to the consultants. He has covered the field thoroughly, and I am sure that the experiences in the Fourth, Fifth, and Ninth Service Commands will run parallel to those of Colonel Coley in the Eighth Service Command.

CAPTAIN WALTERMAN WALTERS, MC, USNR (Corona, Calif.) I recently had the pleasure of accompanying Colonels Coley and Penberthy and Lieut. Col. Griswold on some of their inspections to various United States Army hospitals. I can concur in the statements which they have made, and I think members of the American Surgical Association, who have had an opportunity to visit some of the Army or the Naval hospitals, would be equally pleased to see the very fine type of medical and surgical practice which is being carried out in them. One does not need to wonder at it, when one realizes that the supervision and the consultation of the surgical services are under men of the type whom I have mentioned, who are members of this Association and who, I might say, are directly responsible for the character of the surgical work in those hospitals. I do not think we need to worry about the type of surgical treatment which the soldiers and sailors are receiving in the Army and Navy hospitals.

A word about the Naval hospitals. We have a little different system of medical and surgical consultation and supervision. The President of the United States appointed a group of honorary consultants—on recommendation of Admiral McIntire, the Surgeon General. Among them Doctors Lahey, Balfour, Dandy, Wiener, Lowsley and the late Doctor Crile—Admiral McIntire has had them visit and inspect the naval hospitals. That does not mean just a cursory examination of the physical properties of the hospital. It means an examination of patients, of records, of medical and surgical personnel, etc.

In addition, you might be interested to know that in the Naval hospitals a monthly report of patients, their diagnosis and disposition is obligatory on the part of the commanding officer, which is made out and sent to the District Medical Officer, who, in turn, sends it to the Surgeon General of the Navy. Almost without exception postmortem examinations are routinely obtained.

Now about the methods of receiving information on the advances in medicine and surgery. The Navy has a medical bulletin,* which is published bimonthly, which contains much of the latest and more recent important work in military or Naval medicine. In addition, Navy Medical Officers receive a bulletin every second week from the

* United States Naval Medical Bulletin

Bureau of Medicine and Surgery † in which are reports of the researches of chemical investigation by Naval and civilian doctors, and reports from the Committee of Surgery of the National Research Council. The work of the National Research Council in furnishing the Medical Corps of the Navy and the Army with this very important information, a part of which you have heard today, has helped to improve the treatment which Naval patients are receiving.

At the Naval hospital at which I have been stationed for about a year, we have two staff medical meetings a week, one in which we show moving pictures of various types of operative procedures, with the presentation of a medical paper by alternating members of the staff. At the second meeting abstracts and reviews of the medical and surgical literature are presented.

There are several Army installations around us, and the Army medical officers attend our medical meetings and we theirs. Further evidences of collaboration between the medical officers of the Army and the Navy is the report that after the Naval and Marine casualties were taken care of at Guadalcanal and evacuated some of them were sent to an Army hospital based on one of the islands in that group and to Naval medical hospitals based on other islands there were many Army patients in addition to those from the Navy.

I have enjoyed Colonel Cole's paper very much. I enjoyed being with him on some collateral duties as well as with the other men I have mentioned, and I think it is a credit to the Army Medical Corps that they have asked men of that type to serve as consultants and advisers.

COLONEL BRADLEY L. COLEY, MC (closing). I would like to say a word about graduate medical education as we conceive of it in the hospitals of a Service Command. We believe that efforts to provide every facility which may aid in elevating the level of medical practice in Army hospitals is one of our most important obligations. Towards this end, we have instituted a program which will embody the following: Experimentation with libraries in order to determine what constitutes the smallest acceptable library which will give definitive information concerning all types of medical and surgical cases, instituting clinicopathologic conferences of the type used at Massachusetts General Hospital, and inviting nationally known specialists in the major fields of medicine and surgery with the express purpose of their participating in an informal way in all the activities of the station hospitals during their stay.

In closing I would like to urge the members of this Association, who may play a part in shaping the courses of War-Time Graduate Medical Education, to consider, insofar as Army Hospitals are concerned, the desirability of emphasizing the direct contact, on an informal plane between the teacher and the medical officer. It has seemed to us that by this method, which involves grand rounds, attendance at clinical conferences and free discussion of actual clinical problems arising in each individual hospital, more is accomplished than by formal lecture courses from the rostrum.

† Bumed News Letter (Navy Dept.) (Abb. for "Bu Med & Surg"—The term "Bumed" is correct—STP)

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THE SURFACE TREATMENT OF BURNS*

A COMPARISON OF RESULTS OF TANNIC ACID,
SILVER NITRATE, TRIPLE DYE, AND VASELINE OR BORIC
OINTMENT AS SURFACE TREATMENTS IN 150 CASES

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AND
STANLEY M LEVENSON, M D
BOSTON, MASS

DURING THE PERIOD August 6, 1942, to March 10, 1943, there were 212 cases of burns given surface treatment by one of three standard methods at the Boston City Hospital. All of these cases were serious enough to warrant admission to the wards of the hospital. Of them, 109 came from the "Cocoanut Grove" disaster and 103 at other times. Certain cases have been excluded from the present report because there is no way of using them in evaluating the efficiency of surface treatment. The largest group of these exclusions are 33 "Cocoanut Grove" cases and four other cases that had severe respiratory involvement as well as external burns, and whose death was so largely contributed to by the respiratory factor that evaluation of surface treatment was impossible. All of these deaths occurred within 12 days after injury.

Other groups excluded are patients who were discharged early and "lost" at a time when the depth of the burn could not be estimated, and a few cases who came to the hospital over 48 hours after their burn and cases where other than standard primary surface treatments were used. There remain 150 cases that form the basis of this report. Experimental surface treatments were used on certain areas of some of these cases. The results of the treatments to these areas are not considered in this report. No experimental primary treatments were used on any of the cases from the "Cocoanut Grove" fire.

Table I shows the age and sex distribution of these cases.

The sporadic cases of burns admitted to the wards of this hospital are due to many agents and the patients are of all ages from infancy to extreme old age. Usually about half the patients admitted are children and half of

* From the Burn Assignment of the Surgical Services of the Boston City Hospital, and the Department of Surgery, Harvard Medical School. The work described in this paper was done, in part, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.

† Now Lieutenant, M C, A U S

TABLE I
STUDY OF SURFACE TREATMENT
DISTRIBUTION OF CASES BY AGE AND SEX

Ages	Male		Female		Total		Total
	C	G *	Other	C	G *	Other	
0-4	0		17	0		19	19
5-9	0		10	0		14	11
10-19	2		10	2		13	17
20-29	21		1	16		2	39
30-39	10		4	8		9	27
40-49	2		9	0		13	15
50-59	1		5	0		8	9
60-69	0		2	0		5	5
70-79	0		0	0		1	1
Unknown	1		1	2		1	4
Total	37		59	28		85	150

*Cases burned in the Coconut Grove disaster

them adults. About half the burns are caused by scalding with hot aqueous fluid (water, tea, coffee, soup, etc). About 40 per cent are flame burns. The remainder are burns from miscellaneous causes such as hot oils and greases, molten metal, hot nonmolten metal, acids, other chemicals and electric flashes, etc. The patients are usually from the poorer economic strata of the community and a fair percentage are poorly developed, poorly nourished and anemic. Adults burned in bed or whose clothing has been on fire are frequently intoxicated and many of them are in a state of chronic alcoholism.

In sharp contradistinction to the usual group of patients were those burned in the Coconut Grove disaster. They were mostly young adults in excellent physical condition. Very few, if any, were under the influence of alcohol. It has been estimated that the average patient in this group had consumed the equivalent of two cocktails (25 cc of pure alcohol) during the three hours preceding the fire. There was only one known chronic alcoholic among these cases. All of these burns were flame burns and none of them scalds.

CLASSIFICATION OF BURNS

For the purpose of this report only second and third degree burns are discussed. Second degree burns include all burns no matter how deep, that destroy only a part of the epithelium. Third degree burns include only those that destroy the whole epithelium. The appearance of the burn on admission and for some time thereafter is frequently not a reliable guide to the depth of the burn. However, many small blisters, slight edema of the skin, weeping of broken blebs with a pinkish color of the corium under the blebs, indicate the presence of a second degree burn. On the other hand, charring, dry dead white, or brownish, leathery appearance without edema below it, indicate the presence of a third degree burn. There is, however, a rather large group of cases that cannot be finally classified until they are either well on toward healing in the case of second degree, or granulating in the case of third degree (Fig 1 A-D). This study is based entirely on a classification of the cases at a time after the injury when an accurate estimate as to

depth and of the areas involved in each depth could be made. The percentages of body area involved were calculated by the use of Berkow's¹ formula

PRELIMINARY TREATMENT

On entering the accident floor the patients were seen by an admitting physician, given suitable doses of morphine, and undressed. Ordinarily, patients without shock were sent to the operating room for prophylactic plasma therapy, if needed, and initiation of surface treatment. A few very severely burned patients were sent to the "shock room" of the accident floor and treated there until death or beginning recovery. The Coconut Grove patients were given morphine in the accident floor as usual but they were not undressed until they arrived in the operating room or the wards. About 35 of these patients were treated in the operating rooms. The rest were placed in bed in the wards and treated there, because of limited operating room facilities.

TANNIC ACID-SILVER NITRATE TREATMENT

The tannic acid-silver nitrate treatment was used only on burns of the body, legs, and arms. A rapid tanning after removal of loose debris and washing was made according to the accepted treatment described in the U. S. Army Manual.² Freshly dissolved 10 per cent tannic acid solution in water was applied to the whole area. Then the remainder of this solution was added to an equal amount of 10 per cent silver nitrate solution making a solution of 5 per cent of each. This was applied at once and every half hour for four applications. Anesthesia for the cleaning was used in some cases, particularly in young children. After the fifth application of the tanning solution, a dry, firm, rather than, moderately elastic eschar was formed. A cradle with moderate heating by electric lights was used to promote the drying. Sterile sheets were not used. If the eschar remained intact and clean it was allowed to remain until it came away spontaneously. This occurred only in a few second degree burns. It was found that these eschars were relatively impervious to moist solutions once they had dried out. In all the third degree cases signs of softening with infection under the eschar appeared in from four to eight days (Fig. 1 A-D). The eschar was excised over such areas and secondary treatment initiated.

TRIPLE DYE TREATMENT

From the beginning of the study until the night of the Coconut Grove disaster, no dye treatments were used. But for many years previously, as a result of the important investigations made by Aldrich,³ "triple dye" had been the treatment most used in this hospital for severe burns. For two reasons it was used extensively on the patients from the Coconut Grove. Supplies of silver nitrate were rapidly exhausted and many staff surgeons not connected with the Burn Assignment were called in and were permitted to use the dye treatment with which they were most familiar. In the six weeks following the disaster a few additional cases were also treated in this way.

Triple dye is a water solution containing gentian violet, methyl green and acriflavine. It is claimed that when properly used it has bacteriostatic properties against both gram-positive and gram-negative organisms. Aldrich⁴ has recently advocated its use without previous cleaning unless gross soiling of the burn has occurred. In the present cases a moderate amount of cleaning (breaking of blisters and removal of loose sheets of broken epidermis) was carried out in many cases. In some, soap and water washing of the surface was also done. On the night of the disaster many cases were treated with applications of this dye to burns of all parts of the body including hands and face. During the period of application the patient was protected from the contact with bed clothing by a cradle with lights and the solution was brushed on with a sponge every one-half to one hour. An eschar was formed much more slowly than with tannic acid-silver nitrate, and applications were continued up to 24 hours in most cases and to 48 hours in some (Fig 3 A-E).

These eschars are much more sensitive to moisture than the tannic eschars. They soften and break down rapidly not only on application of ointments or saline dressings but also as a result of lying on them for a very few hours. If softened as a result of moisture without grease, they may, however, be repaired by a further application of the dye followed by a further period of drying. Even after infection has been established on the granulating surface under the eschar, the surface may be wiped and redyed. Such a secondary eschar is not as satisfactory as the original one but it does cover the open surface to some extent. However, such areas must be inspected daily and collections of pus unroofed and the granulations redyed.

1A Flame burn after cleaning and before tanning. Note that the apparent depth of the burn of the left buttock and of the right calf seem to be equal. The small wounds were biopsies.

1C Twelfth day. The eschar was excised daily where it softened and saline dressings were applied. The infection became mixed and later the child lost much weight. Note the similar appearance of the necrotic tissue under the eschar of the two buttocks.

2A Seventh day, at the first change of dressing after treatment with vaselined gauze and a firm voluminous dressing.

2C Twenty-third day. Small Thiersch grafts put on part of the granulations as an experiment.

1B Fourth day, after tannic acid-silver nitrate. Close inspection shows a "blister" on medial edge of right buttock. The fluid from this cultured colon bacilli.

1D Twenty-eighth day. The left buttock is healed indicating that this area was a second degree burn, but the right burn was third degree even on the calf. In this case the first sure evidence of depth of burn was after three weeks. Recovery without deformity followed Thiersch grafting. Final determination of area of burn was second degree, 6%, third degree, 10%. The burn extended beyond the limits seen on any of these photographs.

2B Twelfth day. The same treatment was continued.

2D Twenty-ninth day. The grafts are alive and remained so. Further grafting was done later. Final determination of area of burn, second degree, 4%, third degree, 16%.

1A



1B



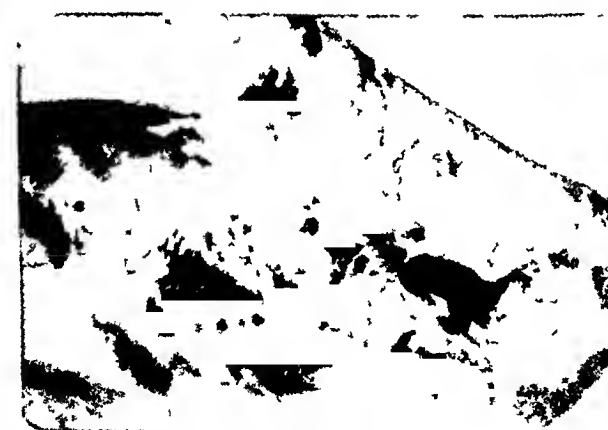
1C



1D



2A



2B



2C



2D



FIGURE 1—M F, age 10, admitted August 24, 1942
FIGURE 2—F P, age 40, admitted February 3, 1943

MIXED TANNIC ACID AND DYE TREATMENT

In some of the Cocoanut Grove cases eschars were started with tannic acid-silver nitrate and completed with triple dye. This procedure was never used at any other time. Since such eschars seem to have more of the physical characteristics of the underlying tannic acid-silver nitrate than of the overlying triple dye, they are classed with the other tannic acid eschars.

OINTMENT TREATMENT

Autoclaved strips of fine-mesh gauze impregnated with vaseline and of wide-mesh scrim impregnated with boric acid ointment were used for the treatment of many areas of burns of the hands, face, feet, or genitalia of all patients otherwise treated with tannic acid-silver nitrate and of some patients treated with triple dye. Such ointment dressings were also applied to the bodies, arms and legs as the only treatment of other patients (Fig 2 A-D). Until after the experience at the Massachusetts General Hospital in treating other victims from the disaster became known,⁷ burns treated in this manner were always debrided and cleaned before the application. Commencing in February, many of the cases were treated with vaseline without cleaning (Fig 2 A-D). Pressure dressings of the type and efficiency described by Allen and Koch⁶ were not used except for a few cases. Burns on the faces of some cases were treated by the application of vaseline or boric acid ointment unsupported by gauze of any kind. No difference in results have been observed distinguishing vaselined gauze from boric acid ointment. For the purpose of this study they are both tabulated under the heading "ointment."

SECONDARY TREATMENT

Vaselined gauze, boric ointment gauze and saline boric acid or weak Dakin's solutions were the chief applications used in secondary treatment. In general, if good progress was being made with ointment dressings these were replaced at intervals of five to seven days until healing or the necessity for grafting was demonstrated. When the time for grafting approached a change to frequent moist dressings was made. Tannic acid eschars on deep burns frequently had to be removed at the end of the first week because of underlying infection. This was done in part by application of vaselined gauze or wet dressings. Many of the triple dye eschars were also removed in the same way at an early date. One patient in the Cocoanut Grove group with a 20 per cent area of third degree burn, became very toxic, and it was thought that infection under the eschar was responsible. The eschar was being removed by vaselined gauze and saline dressings. At one dressing an overenthusiastic application of sulfanilamide powder resulted in typical sulfanilamide toxemia, with cyanosis. The plasma sulfanilamide level rose to 20 mg per cent. Sulfanilamide powder was utilized in this manner only in this one case. In a few cases triple dye eschars were retained for several weeks, repairing any softened areas by redyeing (Fig 3 A-C). This was

done only in patients that were so toxic that any change in treatment was felt to be dangerous

All the patients with second degree burns suffered very little pain at any time following the first dressing, but most of the patients with third degree burns suffered greatly and became extremely sensitive to very slight trauma. This was especially true if wet dressings were allowed to become partially dry before changing. Some of the more severely burned patients were given morphine or general anesthesia at the time of some dressings. Because of pain a few patients were treated with sulfathiazol ointment, cod liver oil ointment and with "eusol" solution primarily because of the good psychic effect that frequently follows a change of method. Some of the patients felt that these changes were beneficial as far as pain was concerned. No other benefit was observed.

A few cases with deep burns of the hands and forearms had slow separation of their sloughs. Their dressings were often very painful. In eight instances Bunyan envelopes⁷ were used as a means of supplying irrigation with saline solution or Dakin's solution. This method of treatment at this stage was successful in relieving a large degree of the pain in six out of the eight patients so treated. It has been recommended that the fluid be drained periodically. The cycles used varied, with the period of filling from 20 minutes to one hour and the empty period from two to four hours. Bunyan advocated the instillation of oxygen when the fluid was out in order to keep the membrane from contact with granulations. Most of our patients preferred not to have the oxygen instilled, as they were more comfortable without it in spite of the fact that the upper surface of the empty bag lay against the granulation tissue.

Splints were used early and freely in burns of the forearm and hand and occasionally for burns of the legs. The splints served to reduce the amount of pain and to rest the part by reducing the possible range of motion in the wrists and finger joints and also served to prevent contractures. In the early days after the Coconut Grove disaster, a straight anterior splint with the fingers extended was applied to many patients with deep burns of the posterior aspect of the hand and fingers. From the point of view of pain, this was certainly useful, but it is very doubtful that this form of splinting should be used in the future, because posterior contractures occur rapidly. Splinting in the neutral position may avoid part of this difficulty.^{8, 9}

* Edinburgh University solution—equal parts of liquid petrolatum and a solution containing 1.25 per cent boric acid and 1.25 per cent calcium hypochlorite, emulsified immediately prior to use.

† These envelopes were kindly furnished by the Union Carbide and Chemical Corporation.

THE RELATION OF SHOCK AND HEMOCONCENTRATION TO SURFACE TREATMENT

Death from shock occurred in only one instance. This was in a patient with flame burns of 60 per cent of her body surface treated with tannic acid-

silver nitrate, who received a very inadequate dose of plasma, 1000 cc, quite large amounts of electrolyte solutions intravenously, and died at 22 hours

Tannic acid-silver nitrate treatment controls surface leakage after it has been applied Triple dye controls it more slowly Vaseline gauze without pressure allows it to continue until it stops spontaneously None of these treatments controls the subcutaneous loss of plasma which may be very large in amount and in fact may be much more important than the surface ooze It is possible that well applied pressure dressings do control this loss and the loss through the surface to some extent,¹⁰ particularly on the hands and forearms Subcutaneous edema is most marked in the face and very difficult to control by pressure⁵ No effort was made to control it in this group of cases The maximum swelling was seen at 24 hours At seven to ten days it had disappeared entirely

Careful washing was used regularly up to the night of the disaster for all cases After it, it was used less and less, and given up entirely as soon as the good results of ointment and pressure treatment without scrubbing that were secured by Cope⁷ became known That cleaning itself can add to shock is understandable First, it may entail a fair amount of manipulation and either pain or anesthesia, both of which are harmful But most important, it frequently may start up a very visible surface exudation that had previously ceased Further discussion of these important matters will be made in other articles^{11, 12}

3A A very satisfactory "triple dye" eschar on the thirteenth day How much of this burn is third degree?

3C Hands on the 32nd day The original treatment of the two hands was the same The eschar was deliberately removed from the left hand but not from the right by wet dressings started one week before this picture This indicates that readiness for grafting in eschar-treated cases depends to some extent on the time that secondary treatments are started

3E Back on 64th day, 17 days after a completely successful grafting of part of the area Note, here also, that whether a burn was second or third degree could not be told until the eschar was removed Final determination of area of burn, second degree, 10%, third degree, 20%

4B On the fifth day Notice that much blistering had occurred under the dressing This indicated a gentle debridement at an early hour It also indicates that it may be as difficult to distinguish early between a first and a second degree burn as between a second and a third degree burn This dressing was removed unusually early in order to see the results of treatment

3B On the 19th day, saline dressings were started This is its condition on the 21st day

3D Back on the 37th day This area was ready for grafting prior to this time but delay was necessary because of poor general condition

4A After cleaning This burn was due to hot water

4C Eleventh day The burn is nearly healed and was healed and dry on the fourteenth day Pigment returned later This was a second degree burn of rather superficial nature and of remarkably even depth Final determination of area of burn, second degree, 20%, third degree, 0%

3A



3C



3E



FIGURE 3—A D, age 30, admitted November 28, 1942
FIGURE 4—P F, age 20, admitted January 21, 1943

POSSIBLE TOXIC EFFECTS OF SURFACE AGENTS USED

Very recently instances of tannic acid poisoning have been reported^{13,14} In general, such reports have incriminated slow methods of tanning rather than the rapid tanning used in these cases. No instances of central necrosis of the liver have been seen in any of the cases in this series coming to autopsy. Neither triple dye, boric acid ointment, nor vaseline have ever been shown to be toxic. One patient, mentioned above, had a temporary toxic level of sulfanilamide from surface application of this drug.

One death only in this series occurred in the interval of time during which Wilson¹⁵ considers deaths from burns to be toxic deaths. This patient was treated with tannic acid-silver nitrate. She died on the fifth day with thrombocytopenic purpura, anemia, edema, azotemia and anuria.

INFECTION IN SECOND DEGREE BURNS

There were 75 cases in the present series having only second degree burns. These varied in area from just under one per cent to 20 per cent of the body surface. Seven were treated with tannic acid-silver nitrate alone, 59 with vaseline alone, one with triple dye, and eight with triple dye on some areas and vaseline on others. Many of these patients, burned in the Coconut Grove disaster, had additional pulmonary damage. About half of the whole group had temperatures of 101.0°F, or more, some time in the first three days, and a few reached 103.0°F for a few hours during this time. The other half had normal temperatures at all times. All of the cases with an early rise had essentially normal temperature charts from the third day to complete healing of the burn with five exceptions. Two children had fever associated with upper respiratory infections and one child had a febrile reaction from the administration of serum. One unexplained rise of temperature to 105°F on the fourth day occurred in a seventy-year-old woman. It is presumed that this fever, which lasted for 48 hours and suddenly receded, resulted from infection with a new organism that entered the burn, although there was no sign of cellulitis, lymphangitis or of intercurrent infection. In one man the temperature rose on the 14th day to 102.0°F, just before healing became complete, and this reaction was associated with lymphangitis. A culture from the burn at this time demonstrated a beta hemolytic streptococcus. These two infections both occurred in vaseline-treated cases and both subsided promptly on treatment with sulfadiazine, and did not delay the healing of the burns. In the first case no prophylactic sulfadiazine treatment had been given, but the second case had had full doses of sulfadiazine for eight days. Half of all these cases had been given oral sulfadiazine for 8 to 21 days beginning at 12 to 36 hours. This incidence of three per cent of clinical infection in 67 cases treated in whole or in part by vaseline, and of no infection in seven tannic acid treated cases, and eight treated with triple dye, indicates these treatments are safe treatments from the point of view of infection in second

degree burns even when sulfadiazine is not given as a precautionary measure. It also indicates that infection was not an important problem in these cases with second degree burn only. The patient with the largest area of purely second degree burn (scald) had 20 per cent involvement. Treatment was with vaselined gauze in large part and an experimental treatment in smaller part. There was never any fever (Fig 4 A-C).

HEALING OF SECOND DEGREE BURNS

The end-point of healing in second degree burns, used as a criterion in the various cases treated, is the time when intact epithelium without crusts or sloughs adhering to it covers the whole area of the burn. Table II presents this data for the cases in this series. More areas are tabulated than there are cases because in many instances more than one kind of treatment was used and different areas had different end points. For instance, in an extreme case four areas might be studied on one patient. Second degree areas in cases also having third degree burns are included.

TABLE II
STUDY OF 150 BURNS

Area Involved	Face		Back		All Other	
	No. of Areas	Av. Time (Days)	No. of Areas	Av. Time (Days)	No. of Areas	Av. Time (Days)
Ointment	68	11	7	19	90	15
Tannic-silver	0	—	6	27	19	24
Triple dye	4	13	8	25	19	16
All treatments	72	11	21	23	118	18

Table II shows that irrespective of treatment, healing of the face is rapid, of the back slow and the rest of the body, intermediate. It does not show any shorter healing time of those burns treated with ointment over that obtained with triple dye except, possibly, in burns of the back. The slight advantage of ointment over tannic acid in length of healing time extends to all areas studied.

Reasons for the rapid healing of the face and slow healing of the back can only be speculative. In favor of rapid healing of the face is a copious circulation, possible conditioning of the skin to thermal trauma by exposure, a firm connection to the underlying tissues, numerous subcutaneous glands of epithelial origin, and relative freedom from trauma during the period of healing. The main reasons the back may heal slowly are that the skin is thick and, therefore, a burn which is deeper than is possible in other areas may still be a second rather than a third degree burn, and that, during healing, trauma (from lying on the back) may be frequent. These burns cannot strictly be compared with those of other areas.

Further analysis of the available data permits the following additional statements to be made:

1. Areas of pure second degree burn heal no more rapidly than the areas of second degree burn associated with areas of third degree burn.

2 Areas of second degree burn heal as rapidly when extensive as when small, within the limit of size observed (20 per cent of body area)

3 Second degree burns of the anterior part of the body, buttocks, thighs, legs, feet, arms and hands all give the same range and average time of healing. The number of cases of burns of the palms of the hands and soles of the feet is too limited to allow any judgment as to healing of this specialized skin.

4 The range of time of healing varies directly with the depth of the second degree burn. This range is narrow for the face, five to eighteen days, and wide for the back, seven to fifty days irrespective of type of treatment. All other burns show a range of healing of six to twenty-four days with either ointment or triple dye treatment, but a wider range of sixteen to ninety days with tannic acid-silver nitrate.

5 Second degree burns from scalds take as long to heal as those from flame burns. Scalds, however, have caused much wider areas to be involved in second degree burns without any parts of the burn being of third degree depth than have been seen in this series to result from flame burns.

INFECTION IN THIRD DEGREE BURNS

It is widely known that bacteriologic asepsis cannot be maintained for any length of time in third degree burns no matter what treatment is used. This infection is frequently very serious. Even under the most meticulous aseptic conditions staphylococcal infections are nearly universal and streptococcal and colon bacillus infections numerous.¹⁶ In general, cultures taken from the infected surface of a burn show mixed infections. This is true of the cases in this series.

Infection occurs in or under the dead sloughing skin or eschar and always permeates or extends under it in time. For this reason it is important to consider the surface area exposed to toxic absorption. Table III shows the extent of third degree burns in the cases studied in this series.

All these patients received sulfadiazine beginning at 12 to 36 hours and continuing for fairly protracted periods of time. Very little important infection occurred in the 57 cases with nine per cent of area or less of third degree burns. Two children contracted a scarlet fever rash three days after the burn, probably not related to the treatment. Seventeen others had fevers of over 101°F at some time after the first week. But in all these cases the fever lasted only a few days. None of these patients died.

The aseptic precautions taken on these cases were not as strict as might be desired. But certain essentials were rigidly carried out. If dressings were used they were large occlusive dressings infrequently changed. Attendants were masked and the careful aseptic technic was used when dressings were changed. The relative freedom from severe infection in these cases confirms the findings of Lyons,¹⁶ that if pathogenic bacteria are present on the original surface of the burn they will die out rapidly under innocuous dressings and rest. Therefore, efforts should not be as much directed toward

SURFACE TREATMENT OF BURNS

TABLE III
STUDY OF 150 BURNS

AREAS INVOLVED IN CASES WITH MIXED SECOND DEGREE AND THIRD DEGREE BURNS

Total Area Burned % of Surface Area	Third Degree Burn % of Surface Area	Cases from		
		C G	Other	Total
0-9%	0-1 5%	12	13	25
	2 0-6%	8	11	19
	Total	20	24	44
10-24%	0-2 5%	2	0	2
	3-6%	2	5	7
	7-9%	2	1	3
	10-16%	1	3	4
	Total	7	9	16
25-49%	5-9%	1	0	1
	10-19%	2	2	4
	20-24%	4	1	5
	25-35%	0	1	1
	Total	7	4	11
50% plus	45-49%	1	1	2
	55%	0	1	1
	No Estimate	0	1	1
	Total	1	3	4
Grand Total		35	40	75

killing bacteria necessarily present as to preventing the addition of new pathogenic strains at later dates¹⁷ Attention to dust was not possible in this series

The 18 patients with ten per cent area or more of third degree burn all had important infections, with fever for some time except for the patient mentioned above who died in shock at 22 hours after admission and the patient that died in five days with thrombocytopenic purpura, anemia, edema, azotemia, and anuria The infections occurred irrespective of surface treatment employed and in spite of adequate sulfadiazine treatment

The bacteria cultured from these cases with large area burns were no different from those cultured from the smaller ones The larger the area the greater the constitutional reaction and the greater the loss of protein from the surface All of these patients were definitely sick with fever, high leukocyte counts, loss of appetite, and all the other symptoms of acute infections. However, in no case was there any spreading infection from the edge of the burn into or under the adjacent skin or elsewhere

NUTRITION IN SEVERE BURNS

All the patients with ten per cent of surface area, or more, involved in third degree burns became serious nutritional problems because of the losses of nitrogen in the urine and from the surface, and because of the increased nutritional requirements resulting from infection with fever¹⁸ All patients were started on high protein, high vitamin diets designed to give them double the normal protein intake and five times the normal vitamin

intake This diet contained 140 Gm of protein Vitamin supplements were given to secure the following intakes A, 25,000 units, D, 2000 units, thiamin, 10 mg, riboflavin, 15 mg, nicotinic acid, 200 mg, and ascorbic acid, 300 mg This took care quite adequately of all the cases with second degree burns or of third degree burns up to nine per cent Much higher intakes of protein have been demonstrated to be needed by the cases with larger area burns^{18, 19, 20}

In addition, the amount of nitrogen losses and requirements are definitely proportional to the area of third degree burn This is contrary to the findings of Cope,²¹ and his associates Presentation of data and further discussion of this important subject will be made in another communication¹⁸

ANEMIA IN SEVERE BURNS

Ham,²² and his associates, have shown that there was an early hemolysis with hemoglobinuria in some of the cases in this series Later, a severe and persistent anemia developed This latter finding has been reported by most authors working in this field for many years In this series this anemia was combatted with non and with frequent whole blood transfusions It was very persistent in some cases and 500 to 1000 cc of blood were given weekly for long periods of time²³

RESULTS OF TREATMENT OF THE 16 MOST SEVERE BURNS

Table IV shows the 16 most severe cases divided according to area involved, method of treatment, and result In a few of these cases, minor areas were treated with experimental treatments Such cases are classed according to the treatment of the major part of the burn Also, if vaseline was used on hands or face and an eschar on all other areas, the case is classed according to treatment of the major area

Table IV shows a very striking relation between the size of a third degree burn and the survival of the patient Only three out of 11 patients with 20 per cent, or more, of the surface area destroyed by a third degree burn survived while none of the five patients with ten or 15 per cent of body area so destroyed died This indicates that there is a critical area of third degree burn at about 20 per cent, beyond which the efforts employed in this series have not been able to save the patient No conclusive evidence of the superiority of one type of treatment over either of the others can be derived from statistical analysis of the data

The deaths were all preceded by great loss of weight and strength in spite of dietary measures, transfusions and other supportive treatment The deaths were all relatively late, occurring on the following days after injury, 16, 25, 28, 32, 39, 80, and 157 In all studies of burns treated prior to the advent of plasma, these patients would probably have died of shock or "toxemia" at a much earlier time

HEALING OF THIRD DEGREE BURNS

In a study of the efficiency of primary surface applications to third degree burns the true end-result, that of complete surface healing, cannot

TABLE IV
 STUDY OF 150 BURNS

MORTALITY AFTER THE SECOND WEEK BY AREAS AND BY PRIMARY TREATMENT OF THIRD DEGREE BURNS								
Per cent Area of Third Degree	Ointment		Tannic Acid- Silver Nitrate		Triple Dye		Total	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died
10	1	0	1	0	0	0	2	0
15	1	0	0	0	2	0	3	0
20	1	0	0	5	1	0	2	5
35	0	1	0	0	0	0	0	1
45	0	0	0	1	1	0	1	1
65	0	0	0	0	0	1	0	1
Total	3	1	1	6	4	1	8	8

be used Too many totally extraneous factors such as the technical success of grafting, the number of grafting operations, the severity of infection, the presence of anemia, and the state of nutrition are some of these factors Two possible end-points, neither of which is ideal, may be used as rough guides to the efficiency of any application to such a burn The first is the time of disappearance of gross slough, which is not a sharp end point and somewhat subject to "subjective" errors The second criterion that may be used is not subjective (from the standpoint of statistical analysis), and that is the actual time of performing the first graft As a test of a certain stage of healing this is far from perfect because any given patient may be operated upon too soon and, therefore, fail and another may be done later than necessary due to reasons that have nothing to do with the actual healing process The time of the first successful graft would be a very poor test because the failure of a graft may be the result of technical errors and not due to any factor of unreadiness in the wound During the earlier months of study it was thought that grafts could only be successful if all slough was removed, there was no fever and no anemia, and no clinical infection Later it was found that grafts could be successful even when put on areas of granulation that were surrounded by gross slough, provided the nutritional status of the patient was good, anemia was not present, and clinical infection not too active (Fig 2 A-D)

In addition to these reservations there is another even greater obstacle to the study of the results of any original application to these cases This is due to the impossibility of keeping the secondary treatment of the cases absolutely uniform In general, secondary treatments consisted of applications either of vaseline or boric acid ointment or of saline or weak Dakin's solution or by various combinations of these The time of starting and the frequency of the secondary dressings varied to a large extent according to such uncontrollable factors as the reactions of the patient, the area of the burn, whether general anesthesia was necessary for dressing or not If an attempt is made to classify the cases according to the sequence and frequency of the various dressings the number in each class becomes so small as to have no statistical value For this reason no attempt is made

to correlate the effects the various secondary treatments may have on the time of healing. Because of these same factors Tables V and VI are presented as indicating, in only a very limited way, any effects of the primary surface treatment.

TABLE V
STUDY OF 150 BURNS
HEALING OF THIRD DEGREE BURNS GRAFTED CASES

	F G S—Days			T F G—Days			No of Cases
	Min	Max	Av	Min	Max	Av	
Small ointment	16	28	24	21	72	33	11
Large ointment	21	60	32	21	120	39	8
All ointment	16	60	27	21	120	36	19
Small tannic silver	34	36	35	39	44	42	2
Large tannic silver	36	55	41	43	66	51	4
All tannic-silver	34	55	39	39	66	48	6
Small triple dye	24	38	33	35	62	44	6
Large triple dye	18	60	39	27	119	54	6
All triple dye	18	60	36	27	119	49	12
All small	16	38	28	21	72	38	19
All large	18	60	36	21	120	47	18
Total	16	60	32	21	120	42	37

F G S equals free of gross slough

T F G equals time of first skin graft

Small burns are 3% or less of surface area

Large burns are 4% or more of surface area

TABLE VI
STUDY OF 150 BURNS

HEALING OF THIRD DEGREE BURNS WITHOUT GRAFTING

	F G S *—Days			No of Cases	Healed—Days			No of Cases
	Min	Max	Av		Min	Max	Av	
Vas	14	30	20	14	28	72	44	8
T S	28	45	35	4	—	—	40	1
T D	25	30	28	2	38	64	51	2

*F G S equals free of gross slough

Table V suggests that areas treated with vaseline became free of slough earlier and shows that they were grafted earlier than areas treated by other methods. It also shows that cases with small areas were free of slough and were grafted earlier than larger cases. This is contrary to the findings of Cannon²⁴ in regard to the separation of slough. He had to delay the grafting of his most severe case until the 77th day because of various complications. A similar delay for similar reasons occurred in several of the cases in this series that had comparable or larger areas of third degree burn.

Thiersch grafts were applied in all but two instances. In these exceptions Reverdin grafts were employed. The condition of the patient with 45 per cent of surface area involved would not have permitted a Thiersch operation even if enough suitable donor sites could have been found. Sixty-two per cent of the first Thiersch grafts on all cases grafted were fully successful, 14 per cent partially successful, and 24 per cent failed. All areas treated without grafting were necessarily small and usually consisted of

multiple small areas. The smaller number of cases recorded in Table VI, under healing time, is due to the fact that information concerning some cases was secured by letter or telephone and not by direct observation, and such information has not been used. The table shows that in them there was a more marked difference in favor of vaseline so far as the time required for the slough to disappear is concerned, but essentially no difference in the time of final healing. This is to be expected as the latter is dependent on the exact sizes and shapes of areas and possibly on the efficiency of secondary treatment rather than on the original treatment.

Further analysis of the available data permits the following statements to be made:

1. If Tables V and VI were separated into "Cocoanut Grove" cases and other cases, no difference in results would be found.

2. Deep burns became free of slough after a longer interval than burns that barely removed all epithelial elements. This was particularly true if fascia or tendons were involved, as was true in some of the patients with burned hands.

3. Location of the burned area was not as important as in second degree burns although, again, the thick skin of the back was usually slow to separate even when the underlying fascia was not involved.

4. Third degree burns from scalds, although less common, reacted in no way differently from third degree burns of the same size and depth that were caused by other forms of thermal trauma.

SUMMARY AND CONCLUSIONS

1. One hundred and fifty cases of burns have been studied from the point of view of comparing results following surface applications of ointment, gauze dressings, tannic acid-silver nitrate, and triple dye.

2. There were two slight clinical infections in 75 patients that had second degree burns only, and none of the 75 patients died.

3. Edema of the face disappeared very rapidly without any application of pressure.

4. Skin healing of second degree burns of all areas except the back, took place a few days earlier if ointment or triple dye were used than if tannic acid was used. Skin healing of second degree burns of the back took place a few days earlier if vaselined gauze or boric acid ointment were used for treatment than if either tannic acid-silver nitrate, or triple dye were used.

5. Skin healing of second degree burns of the face was faster and of the back slower than of all other parts of the body.

6. Fifty-seven patients had mixed second and third degree burns with nine per cent, or less of body area involved in third degree burn. There were 19 instances of clinical infection in these cases, but none were serious. None of these patients died.

7 Eighteen patients with more than ten per cent of surface area involved by a third degree burn either died or were seriously ill before recovery

8 One patient died from shock at 22 hours following inadequate plasma administration

9 One patient died at five days with thrombocytopenic purpura, anemia edema, azotemia, and anuria as complications

10 The remaining 16 patients demonstrate that patients with 20 per cent, or more, of surface area involved in a third degree burn have a very critical burn. All five patients with 10 or 15 per cent of third degree burns survived while only three out of eleven with 20 per cent or larger areas survived

11 All the patients who died and many of those who lived with third degree burns of ten per cent area or more, showed infection, severe loss of weight, and critical metabolic disturbances including azotemia, hypoproteinemia, anemia, and abnormally high losses of nitrogen

12 The statistics suggest, but do not prove that vaselined gauze and triple dye treatment were safer for large third degree burns than treatment with tannic acid-silver nitrate

13 Small third degree burns became free of slough and were grafted earlier than large ones

14 Areas treated with vaselined gauze became free of slough and were grafted earlier than areas treated with the other two methods

The authors acknowledge with deep gratitude the enormous labors of the hospital staff, in all grades, and in all departments, and of several other agencies and individuals too numerous to name, without whose help the study of and care of these patients, particularly those from the Coconut Grove disaster, could not have been carried out

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GUNSHOT WOUNDS OF THE ABDOMEN

A SURVEY OF 238 CASES

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PRIOR TO WORLD WAR I conservative treatment was generally advised for gunshot wounds of the abdomen received during battle. In the American Civil War there were 3,690 such cases, with a mortality of 90 per cent¹. In the Spanish-American War there were 44 cases reported. Four were operated upon, and all four died. Of the remaining 40 that were treated conservatively, 25 died, a mortality of 62.5 per cent¹. During the Boer War (1900) and the Russo-Japanese War (1904-1905) these patients were treated by starvation and large doses of morphine². Because of such war reports, the military surgeons in the early days of World War I were of the opinion that practically all cases recovered were not operated upon. The reports from civil life pointed to a more favorable result with early operation. Grant,³ in 1899, collected 253 civilian operated cases of gunshot wounds of the abdomen, with a mortality of 52 per cent.

Early in World War I, Leiche⁴ reported that the mortality with conservative treatment was over 80 per cent, and advised early operation. In 1916, Wallace⁵ reported a study of 1,200 cases of gunshot wounds of the abdomen among the British Expeditionary Forces. In this large group the mortality of the operative cases was 53.9 per cent, which was not strikingly less than the total mortality of 60.2 per cent, including the nonoperative cases. In 1917, Lockwood and Kennedy⁶ reported 500 cases seen in an advanced casualty station. There were 356 operative cases, with a mortality of 51.7 per cent.

In 1924, Condict⁷ reported nine deaths in 20 cases of gunshot wounds of the abdomen seen at the Gouverneur Hospital, New York. In 1931, Billings and Walking⁸ reported 114 cases from Philadelphia, with an operative mortality of 48.2 per cent. Prey and Foster⁹ reported a 68 per cent in 22 cases. McGowan¹⁰ analysed 164 cases of penetrating wounds of the abdomen, of which 64 were gunshot wounds, with a mortality of 59.3 per cent. Oberhelman and Le Count¹¹ reviewed 343 cases from the Cook County Hospital, with a mortality of 61.4 per cent in the operative cases. In 1938, Taylor¹² reported 101 cases of gunshot wounds of the abdomen which included 11 that had been shot with shotguns. There was a mortality of 53.4 per cent for the operative cases of the entire group. In an analysis of 35 personal cases Storck¹³ was able to show a mortality of 40 per cent. In 1941, Rippy¹⁴ reviewed 369 cases that were seen in a 17-year period. Three hundred and thirty-seven of the patients were operated upon, with a mortality

GUNSHOT WOUNDS OF ABDOMEN

of 60.5 per cent. The mortality of 29 of these cases treated in 1940 was 41.3 per cent. He also presented 36 cases of shotgun wounds of the abdomen, with a mortality of 80.5 per cent. More recently, Hamilton and Duncan¹⁵ reviewed 336 cases of penetrating wounds of the abdomen. The total mortality for 190 gunshot wounds was 51 per cent, the operative mortality for 182 cases was 48.9 per cent.

This study is based on 238 patients who were admitted from January 1, 1937, to January 1, 1943 to the Surgical Service of the Emory University division of Grady Hospital, with the provisional diagnosis of gunshot wound of the abdomen. All of the patients were Negroes. Those who died in the emergency clinic before admission to the wards are not included. With this exception, the cases were consecutive. Of the 238 patients included in this series, 29 were shotgun wounds and 209 were produced by rifle or pistol.

Shotgun Wounds—Of the 29 patients wounded with shotguns, two died before any operative procedure could be carried out. Nine patients were not operated upon because it was thought that very few, if any, of the pellets had entered the abdominal cavity and that the small perforations, should there be any, would seal spontaneously. In this group there was one death from pelvic abscess and peritonitis. This death occurred three weeks after admission. One of the unoperated patients required a transfusion after passing fresh blood in the stools. Six of the operative cases required resection of involved intestine, one of these survived, and in this instance an exteriorization and delayed anastomosis was done. Those requiring resection were shot at close range with resulting extensive destruction of the abdominal wall, and often there was serious damage to the liver, kidney, pancreas and large blood vessels. The mortality for the operated group was 55.5 per cent, and the total mortality for the entire group, including the unoperated cases and those that died immediately after admission, was 44.8 per cent (Table I).

TABLE I
SUMMATION OF 29 CASES OF SHOTGUN WOUNDS

	Died Immediately	Operated		Not Operated	
		Died	Improved	Died	Improved
1937			1		1
1938		2			2
1939	1	1			
1940		2	2		5
1941	1	4	2		
1942		1	3	1	
	—	—	—	—	—
	2	10	8	1	8

Pistol and Rifle Wounds—In the group of 209 patients who were shot with pistols or rifles, 15 died before any operative procedure could be carried out. These patients were admitted in severe shock and did not respond to intravenous fluids or transfusions. One patient refused operation and left the hospital against advice, it was thought that his only injury was to the liver. His death was not subsequently recorded. Thirteen patients

were not operated upon because it was thought that the bullet did not enter the peritoneal cavity, one of these died, and autopsy revealed a large abscess in the right paracolic space. One patient was admitted to the hospital with an abscess extending above the umbilicus and pointing in the pelvis, three weeks after having received a bullet wound in the right lower quadrant. She improved after drainage of the abscess. Of the 181 patients in this group who were operated upon, 84 died and 97 were discharged improved, making a mortality rate in the operative group of 46.4 per cent. The total mortality, including those that died soon after admission, was 47.8 per cent (Table II).

TABLE II
SUMMATION OF 209 CASES OF PISTOL AND RIFLE WOUNDS

	Died Immediately	Operated		Not Operated	
		Died	Improved	Died	Improved
1937	4	21	18		3
1938	5	15	17		1
1939	1	11	9		
1940	2	15	18		3
1941	1	16	18	1	1
1942	2	6	17		2
	—	—	—	—	—
	15	84	97	1	12

Injuries Found at Operation—In the group of 181 patients wounded with pistols and rifles who had exploratory celiotomies, a combination of large and small intestinal wounds was found most frequently. Injury to the small intestine alone was next frequent and injury to the large intestine alone was third in order of frequency. The injuries and results are recorded in Table III.

Cause of Death—Seventeen of the 238 patients died immediately after admission, and four died on the operating table. Shock and hemorrhage were striking findings. Forty-seven of the 94 postoperative deaths (50 per cent) occurred within 48 hours. These deaths are arbitrarily classified as due to shock and hemorrhage, pneumonia and peritonitis, or combinations of these. Mason,¹⁷ and Loria¹⁸ have emphasized the influence of hemorrhage on the mortality. Severe blood loss seems to predispose to the development of pneumonia and peritonitis, hence there is much confusion of these factors as the actual cause of death in the early postoperative period. Twenty deaths occurred between the second and seventh postoperative days and with one exception, all were due to pneumonia or peritonitis. The exception was a case with evisceration on the fifth and death on the sixth postoperative day. The late complications and their results are shown in Table IV.

Chemotherapy—Thirty-three of the entire operative group of 199 patients were given sulfanilamide. Fourteen received the drug subcutaneously and 19 received it both subcutaneously and intraperitoneally, the number of deaths was six and five, respectively, making a mortality of 33 per cent. The drug seemed to be of considerable value in controlling the peritonitis. The average amount used intra-abdominally was 5 Gm.

GUNSHOT WOUNDS OF ABDOMEN

TABLE III

TABULATION OF LOCALIZATION AND RESULTS ON PISTOL AND RIFLE WOUNDS OPERATED UPON

	No of Cases	Died	Lived
Stomach	8	4	4
Stomach and small intestine	3	2	1
Stomach and liver	1	1	0
Stomach and kidney	1	1	0
Stomach and pancreas	2	1	1
Stomach and colon	4	3	1
Stomach, pancreas and kidney	1	1	0
Stomach, kidney and spleen	1	1	0
Stomach, colon and small intestine	1	1	0
Stomach and chest	2	2	0
Liver	16	3	13
Liver and kidney	6	4	2
Liver and chest	1	1	0
Liver and colon	1	0	1
Liver stomach pancreas and kidney	1	1	0
Small intestine	37	14	23
Small intestine and colon	32	15	17
Small intestine and bladder	2	1	1
Small intestine bladder and rectum	3	1	2
Small intestine and head	1	1	0
Duodenum and colon	1	1	0
Duodenum and liver	2	2	0
Large intestine	17	8	9
Colon and appendix	1	1	0
Colon and chest	1	1	0
Bladder	3	0	3
Gallbladder liver and stomach	2	0	2
Kidney	3	0	3
Kidney and spleen	2	1	1
Kidney, colon and small intestine	4	3	1
Kidney and chest	1	1	0
Spleen, large and small intestine	1	2	1
Blood vessels			
Aorta and vena cava	1	1	0
Aorta and small intestine	1	1	0
Vena cava and small intestine and colon	1	1	0
Portal vein	1	1	0
Common iliac	1	1	0
No perforations found	7	1	6
No peritoneal perforation	5	0	5
	<hr/> 181	<hr/> 84	<hr/> 97

Diagnosis—In most instances, the diagnosis offers little difficulty. It is desirable to ascertain the time interval between the injury and hospitalization and, if possible, the direction of line of fire. As emphasized by Meyer and Shapiro,¹⁹ the back and sides, as well as the front of the abdomen, should be inspected and palpated carefully. When there is no wound of exit, frequently the bullet may be felt immediately beneath the skin at some distance from the point of entrance. Eisberg²⁰ has called attention to the need for careful study of the point of entrance in order to determine the direction of the bullet. When the bullet enters the skin obliquely, an area of abrasion appears on the proximal side of the wound and an area of undermining in the subcutaneous tissue. Muscle rigidity may be absent or as pronounced as that found with ruptured viscus. Palpation of the umbilicus or palpation of the pelvic peritoneum by rectum

TABLE IV

LATE POSTOPERATIVE COMPLICATIONS OTHER THAN PNEUMONIA AND PERITONITIS

	No of Cases	Deaths
Postoperative obstruction requiring operative relief	5	2
Pelvic abscess	8	5
Empyema	3	3
Liver abscess	2	1
Subdiaphragmatic abscess	1	0
Pylephlebitis	1	1
Postoperative evisceration	5	1
Granuloma of lung	1	1
Arteriovenous fistula (femoral) postoperative gangrene of leg	1	1
	—	—
	27	15

will reveal cases with minimum peritoneal irritations. Occasionally, when the internal injury is confined to the chest and associated with a hemothorax, there may be rigidity and tenderness of the upper abdomen. The presence or absence of peristalsis cannot be relied upon, it may be present when there is either blood or small amounts of solid feces present in the abdominal cavity. Many of the cases seen early have peristalsis.

Immediately upon admission to the hospital a urine specimen should be collected and examined for blood. If no urine or only a few drops of blood are found on catheterization, it is probable that there has been a perforation of the bladder. Roentgenologic examinations are helpful in many instances. They may indicate the position and probable course of the bullet or may reveal the presence of free air in the peritoneal cavity, and thus influence the location of the incision. Some patients have practically no abdominal findings except the wound of entrance, therefore, it is best to explore the wound of entrance to determine the depth and direction of penetration or to explore the abdominal cavity if it is at all possible that the bullet had entered it. To await signs of peritoneal irritation is not justifiable. Peritoneoscopic examination has been advocated by Hamilton²¹ in questionable cases of penetration of the peritoneum.

PREOPERATIVE OPERATION

Patients in shock are immediately placed in Trendelenburg position. Fluids are administered intravenously in all cases. Many of the patients will require blood or plasma. When urgency demands, Group "o" blood may be given without cross-matching. Morphine sulphate is administered immediately unless the patient is in an alcoholic stupor. Warm blankets and hot water bottles are placed about the patient. A tube is inserted into the stomach through the nose, the gastric contents are aspirated, and the tube is left in place. If sufficient time elapses in the preoperative period, 500 cc of 0.8 per cent (4 Gm) sulfanilamide, is given subcutaneously as the initial dose. Mixed antianaerobic serum and 1500 units of antitetanic serum is administered prophylactically to all patients. Attempts are made to move the patients to the operating room quickly and in the best possible condition. Supportive measures can be continued during the operation.

Anesthesia—Although spinal anesthesia has been advocated for selected

cases, its safety cannot always be predicted Nitrous oxide-oxygen induction followed by ether is safest Some method for aspirating the pharynx and trachea should be available

OPERATIVE PROCEDURE

Wounds of entrance and exit are first excised, treated with sulfanilamide crystals, and packed

Muscle-splitting rectus incisions have been used for all explorations In most instances this is placed on the right side and gives ample exposure to explore the entire contents of the abdominal cavity Occasionally, the left rectus incision, or a transverse incision in the flank, will offer better exposure of the area of greatest damage

Immediately upon opening the abdomen the contents of the peritoneal cavity are aspirated Vigorous bleeding, if present is controlled Usually, bleeding from the liver can be temporarily controlled with moist, hot packs, and bleeding from large mesenteric vessels with digital compression of the root of the mesentery, until clamps can be placed on the open vessels Hemorrhage from wounds of the larger vessels is controlled with digital pressure until the site of bleeding is exposed and sutured Autotransfusions, as suggested by Hamilton and Duncan,¹⁷ may be employed under desperate circumstances

Usually, the cecum is examined first, the small intestine is then inspected from the ileocecal junction to the ligament of Treitz, using warm, moist packs to handle the intestine Any perforations are repaired as they are found Should a resection be necessary, clamps are placed on the open ends as a landmark, while the remainder of the small intestine is examined, thus avoiding the possibility of performing two anastomoses that could readily be converted into a single one without the loss of too large a segment

The large intestine is explored next Solid feces is removed with dry gauze sponges The stomach and retroperitoneal structures are then carefully examined Moderately-sized retroperitoneal hematomata are left undisturbed unless they involve the kidneys, pancreas or duodenum Longer incisions and evisceration, as advocated by McGowan,¹⁰ and Connors²² should be used if areas of injury cannot be exposed adequately Minor lacerations of the kidney or spleen can usually be sutured, otherwise these organs should be removed Most wounds of the liver are not bleeding at the time of exploration, but if active bleeding is present sutures on a large, half-round, blunt needle can be used In some instances it is necessary to use a gauze pack which is brought out through the incision or a stab wound Perforations of the diaphragm (on the left) should always be closed to avoid the possibility of herniation

All perforations in the intestines are freed of protruding mucosa and closed transversely with a running suture of fine chromic catgut, which includes all layers This, in turn, is inverted with interrupted sutures of fine silk Silk has been used on many occasions for the initial line of sutures and no

apparent difficulty has been encountered. However, silk should never be used in bladder mucosa since it may initiate calculus formation.

After completing the exploration and repair of injuries, the peritoneal cavity is again aspirated. No attempt should be made to irrigate the peritoneal cavity. Peritoneal drains are not indicated. Four to 6 Gm of sulfanilamide crystals are dusted into the abdomen. At the present time this seems to be the drug of choice for these cases^{23, 24}. The peritoneum is closed with catgut. The remainder of the wound, including all layers except the peritoneum, is closed with through-and-through sutures of silver wire or silkworm gut. About 1 Gm of sulfanilamide is placed in the incision.

POSTOPERATIVE TREATMENT

The patients are placed in Fowler's position after reaction, unless shock is evident. Constant suction with an indwelling tube is applied to the stomach and 4000 to 5000 cc of fluids is administered daily. Sulfanilamide is given subcutaneously, using 150 cc of 0.8 per cent solution (1.2 Gm) every six hours. Frequent blood sulfanilamide determinations should be made. The appearance of jaundice and anemia are indications for discontinuation of the drug. In the absence of toxic effects, administration is continued subcutaneously until sulfadiazine can be taken by mouth. This usually takes four to five days in uncomplicated cases. When peristalsis is normal, the abdomen soft, and flatus is being passed by rectum, gastric suction can be discontinued and water given by mouth. During the immediate postoperative period oxygen with 5 per cent carbon dioxide is administered every 4 hours to prevent pulmonary atelectasis. Obstruction and paralytic ileus occurring in the early postoperative period respond well to the use of the Miller-Abbott tube. Feeding is begun on the sixth or seventh day. Wound infection, pelvic abscess and subphrenic suppuration should be carefully watched for.

DISCUSSION—The mortality rate in gunshot wounds of the abdomen has remained high (and will probably continue to remain high) because there is always a large percentage of deaths by virtue of extensive damage to the abdominal viscera and large blood vessels. The factors that determine mortality fall into two groups: (1) Those that cannot be influenced by the surgeon's skill and management, and (2) those that can be minimized by greater efficiency in treatment. The severity of the wound, the time required to reach the hospital where adequate therapy can be instituted, and the physical status of the patient prior to receiving the injury are obviously uncontrollable factors. The type of anesthesia, the prompt but complete exploration with repair of damage, the proper use of chemotherapy, and the postoperative management are all factors which are definitely controllable.

Many of the patients considered here were intoxicated and some were in an alcoholic stupor. Their state of nutrition was frequently poor, syphilis and cardiovascular diseases were common. The severity of hemorrhage and shock was controllable to some extent by the prompt administration of

plasma or whole blood, thus allowing the patients to be brought to operation more quickly, and increasing the chances of survival

SUMMARY

1. A statistical review of 238 cases of gunshot wounds of the abdomen is presented

2 The general plan of treatment is discussed

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PRINCIPLES UNDERLYING THE OPERATIVE APPROACH TO THE TREATMENT OF MYOCARDIAL ISCHEMIA*

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I SHOULD LIKE TO RECORD THE RESULTS obtained by my associates and myself on the subject of revascularization of the heart. This work represents the results of several thousand experimental operations upon the heart carried out during the past ten years. I should also like to comment upon the nature of coronary artery disease in reference to the operative approach for its relief. Thirty patients with sclerosis of the coronary arteries were operated upon between the years 1935 and 1938. This small group of patients were regarded as a study group. The clinical results in the patients who survived the operation were satisfactory, and seven additional patients were operated upon before the present war interrupted further application of this work. The results in the patients will be recorded by Dr. Harold Feil.

It is clear to me that the principles underlying the operative approach to this subject must be based upon experiment. The underlying concepts for this approach cannot be plucked out of thin air, no matter how enterprising the surgeon may be. I do not believe it is possible to contribute to these principles in the early stages of this work by operating upon patients. The operation is not based upon extirpation. The surgeon cannot take out the diseased arteries nor can he remove an infarct. The principles underlying the operation must be brought to light by carefully controlled experiment before he justifiably can apply the operation to patients.

One concept which has come out of this experimental background concerns the nature of coronary artery disease. It can be compared with epilepsy. As sclerosis of the blood vessels develops a zone of anoxemia appears. In the heart, as in the brain, an irritable focus or "trigger" appears which can "fire" and destroy the normal physiology. A focus in the brain produces a convulsion, a focus in the heart destroys the coordinated rhythmic contraction and relaxation of muscle fibers and produces ventricular fibrillation. Some fibers are relaxed while others are contracted. The heart cannot expel blood and the patient dies. I need scarcely say that the man who has a trigger developing in the heart usually does not have a failing heart. When it "fires" it is sudden, often unexpected and always final and irreversible.

Another concept which has come out of the experimental work is that of a blood-bath to the trigger zone. By this term is meant an amount of oxygenated blood which (1) will reduce the irritability of the zone

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and prevent it from "firing", and (2) will preserve the viability of heart muscle and prevent it from degenerating into scar tissue

The requirements for a blood-bath cannot be given in cubic centimeters of flow per minute but can be indicated by an illustrative experiment. A trigger can be readily produced by ligation of a number of small arteries leading to a zone of myocardium (Fig 1). In this experiment one small artery after another is ligated and the myocardium supplied by these arteries becomes increasingly cyanotic. For purposes of quantitative illustration, I can say that the zone does not "fire" when five of these small arteries are ligated. The animal can recover from these ligations. However, if an

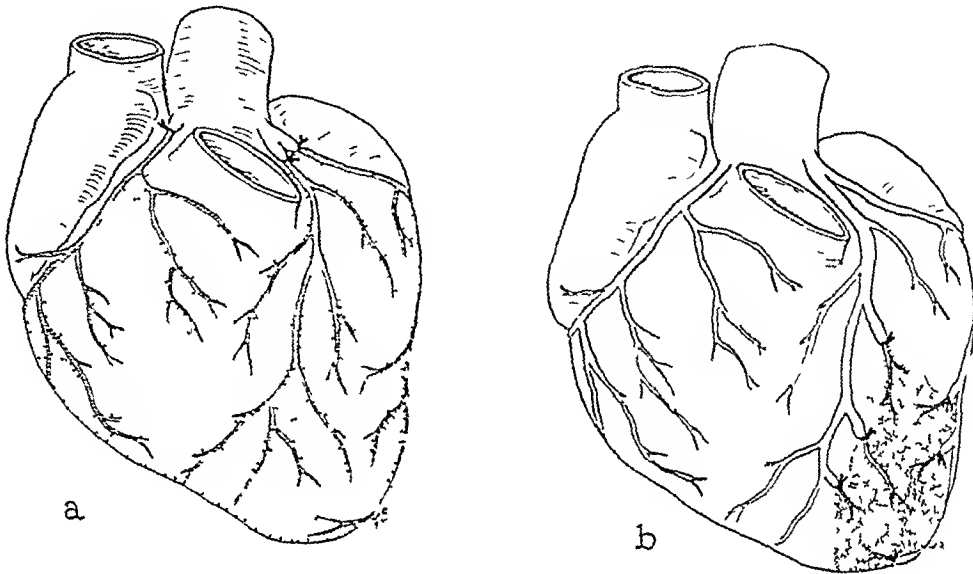


FIG 1.—Two types of coronary artery occlusion.
A Partial occlusion of three major arteries. This may be tolerated by the heart.
B Complete occlusion of six arteries to a small area of the left ventricle. This produces a trigger which in turn produces ventricular fibrillation and death. A blood bath to this area is prophylactic.

additional artery is ligated the trigger does "fire" and the animal is lost. This one additional channel, small as it is (but not insignificant), may be regarded as "the last straw." I think this experiment clearly indicates that a small amount of blood can be effective as a blood-bath. Repeated experiment has emphasized, over and over again, the significance of a small amount of blood delivered to that part of the myocardium where the blood supply is deficient. Those who are adversely critical of this research on coronary artery disease and the surgical approach to its treatment will please bear this point in mind. A small amount of blood can make the difference between recovery and death. Our experiments have shown that there are three methods of approach for the production of a blood-bath (Table I).

TABLE I

A Blood-Bath Can be Provided by Operative Methods

- 1 By establishment of extracoronary communications. This can be done by grafting tissues upon the heart.
- 2 By establishment of intercoronary communications. This can be done in two ways:
 - a By inflammation on surface of heart produced by operative methods. Asbestos produced the most favorable response.
 - b By providing a time factor so that arterial occlusion becomes effective. This can be done by methods 1 and 2a of this outline.

Extracoronary Communications—These are produced by grafting tissues upon the heart. The tissues available are numerous. I can mention pericardium, mediastinal fat, chest wall, lung, diaphragm, stomach, spleen and omentum. We used these various structures experimentally in our early work but the use of some of them is not practical. *My chief concern has not been whether pectoral muscle or omentum should be used but whether vascular communications can be demonstrated by any method and with any tissue.* It is up to the surgeon to show what he can produce in the way of communications and it requires more than a few experiments to make a satisfactory demonstration of these vascular communications. Figure 2 shows some specimens showing these communications. The coronary arteries have been injected with a mixture of barium sulfate and gelatin and the specimens have been cleared by the Spalteholz method. The blood vessels can be readily seen extending from the coronary arteries out into the blood vessels in the grafts that were placed on the heart. There are communications between the heart and the grafts. They are large enough to be seen without magnification. Let us try to interpret these anastomoses in terms of whether they might be adequate to produce a blood-bath.

Intercoronary Communications The coronary arteries are essentially end-arteries. If one coronary artery is injected with a mixture of barium sulfate and gelatin practically none of this mixture passes beyond the arterial bed of the injected artery (Fig 3). If the descending ramus of the left coronary artery is ligated during life and then transected distal to the ligature it will be found that the blood emerging from the artery in a retrograde direction "can be measured only in drops not in cubic centimeters per minute" (Wigger's Text Book of Physiology). This small quantity of blood comes from intercoronary communications. Because of this anatomic arrangement we find that the heart is predisposed to the development of a trigger or an infarct when a major artery is occluded. Conversely, if some communications between coronary arteries are present then one of these arteries can be ligated without producing a trigger and without producing necrosis of muscle. With a full appreciation of the value of intercoronary communications let us inquire into the methods by which they can be produced. Intercoronary communications can be produced in two ways. One is by the production of inflammation on the surface of the heart. The other is by coronary occlusion plus a factor of time.

A—INFLAMMATION ON THE HEART

It occurred to me early in our experimental work that a bed of granulation tissue on the heart would increase vascularity and distribute blood to every part of the heart. I used powdered beef bone to produce an inflammatory reaction, both experimentally and on patients. This was the first attempt to produce inflammation on the surface of the heart. We did not make any measurements of the amount of help this procedure afforded until

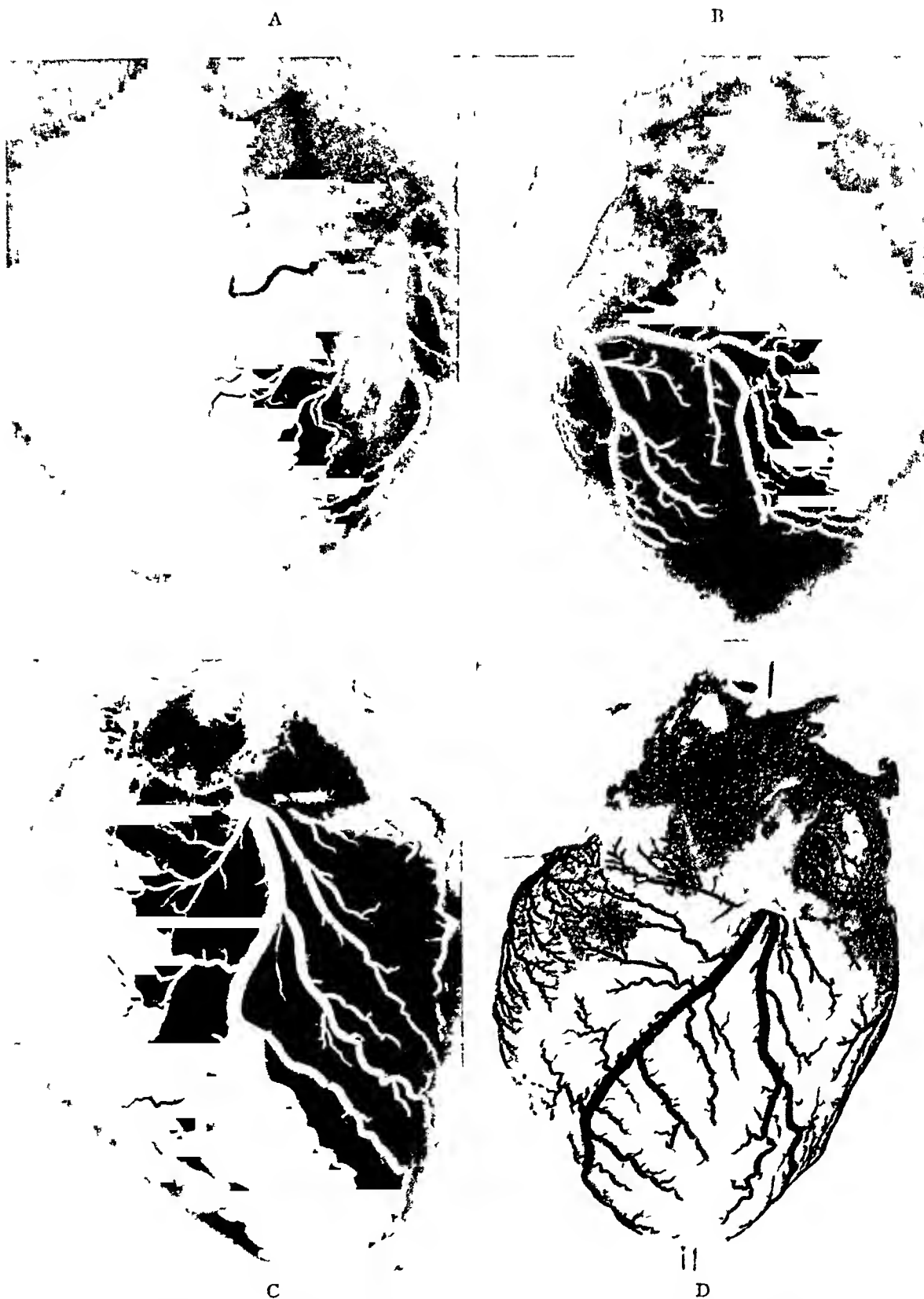


FIG 3—Normal hearts. Coronary arteries injected with mixture of barium sulfate and gelatin. The coronary arteries are practically end-arteries but a few intercommunications can be found in some specimens.

- A. Left circumflex artery injected. Small amount of barium sulfate can be seen in descending branch of left coronary artery.
- B. Circumflex branch of left coronary artery injected.
- C. Common left coronary artery injected.
- D. Three coronary arteries injected.

Stanton, Schildt and myself¹ carried out such studies two years ago. We exposed the heart by operation and then abraded or scraped off the epicardium by special burs made for this purpose. The incision was closed. One to three weeks later the heart was again exposed at operation and the descending ramus of the left coronary artery was ligated at its origin. This experiment was performed on 50 dogs. Ligation of the artery alone was performed in another group of 50 dogs. The mortality in this control group was 70 per cent. The mortality in the group, in which the surface of the heart was abraded at the first operation and the descending ramus

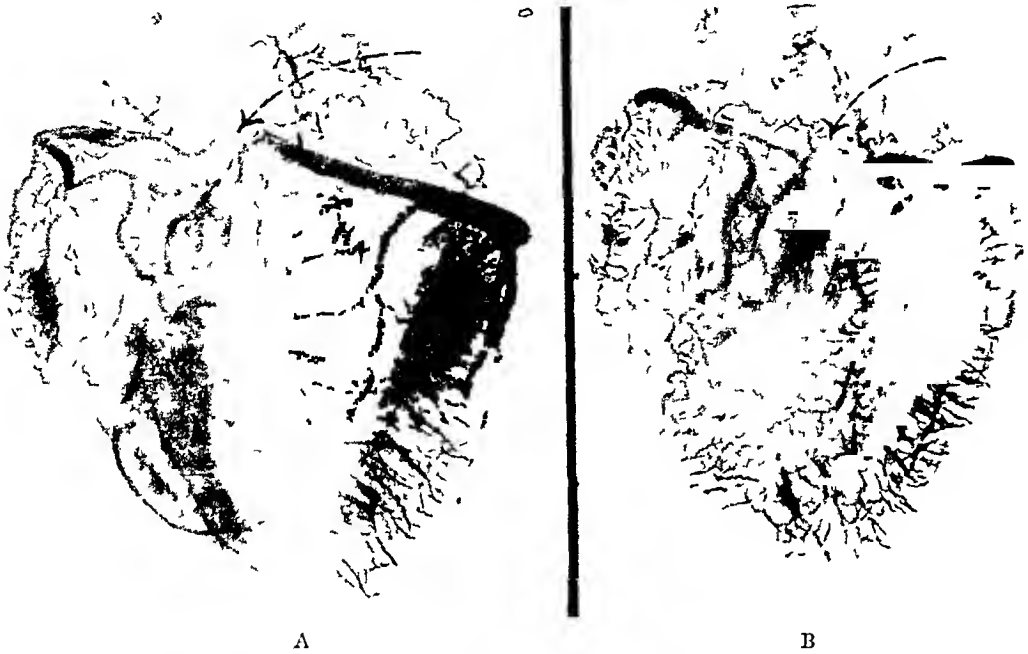
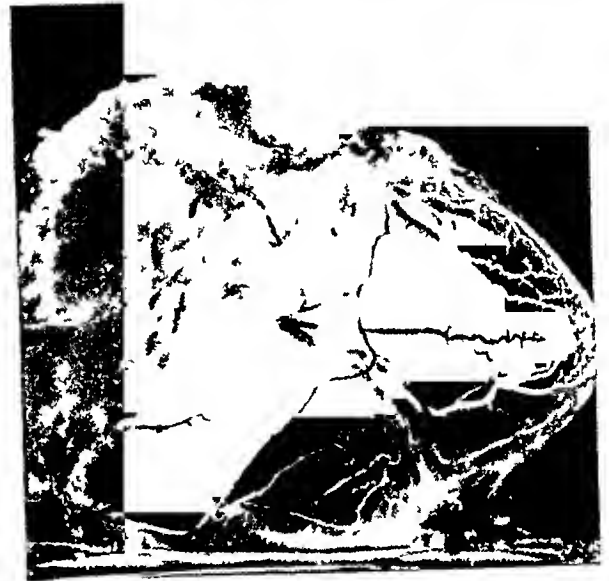
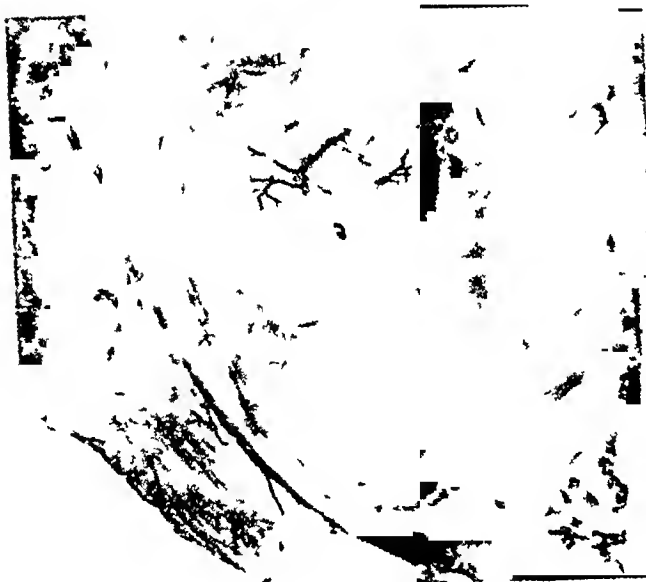


FIG 4—Circumflex branch of left coronary artery and the right coronary artery were injected with a mixture of barium sulfate and gelatin. The descending ramus of the left coronary artery is indicated by the arrow. Note the difference in the injection in these specimens.

A A normal heart.

B A heart the surface of which was abraded at operation two weeks before killing the animal for injection. The degree of injection in the descending artery is an indication of the intercoronary communications present in these hearts. (A) Shows the greatest injection out of a group of ten normal hearts and (B) shows the greatest injection out of a group of ten abraded hearts.¹

of the left coronary artery was ligated at its origin in the second operation, was 38 per cent. We could demonstrate intercoronary anastomoses in many of these abraded hearts (Fig 4) and, indeed, in some of the specimens the infarct was small, or there was no infarct at all, after the artery had been ligated. The absence of an infarct in something that never occurs in a normal heart after ligation of this artery at its origin in one step. This is a simple experiment and I do not see where there can be any misinterpretation of results. Indeed, insofar as the reduction in mortality is concerned, we might note that each of the control group had one anesthesia and one operation while each of the other experiments had two anesthetics and two operations. The difference in mortality is definite and conclusive. One does not like to abrade the human heart because it produces extrasystoles and tachycardia.² Fortunately, it is not necessary to do this at operation because the application of inflammatory agents on the heart



2C

2D

FIG 2—A Epicardium stripped off, asbestos applied, heart brought into contact with chest wall. Specimen five weeks later. Coronary arteries injected. Note extracoronary communications and internal mammary artery. These anastomoses developed without stimulus of coronary artery occlusion. B Substernal muscle with internal mammary arteries grafted on the heart. Arterial occlusion at subsequent operations. Specimen injected through coronary arteries. Note injection of internal mammary and other arteries of graft.

C Heart abraded, brought into contact with chest wall, asbestos applied 16 days later descending coronary artery occluded. Dog killed after three months. Right and circumflex coronary arteries injected. Descending artery filled as did also the internal mammary artery of the chest wall.

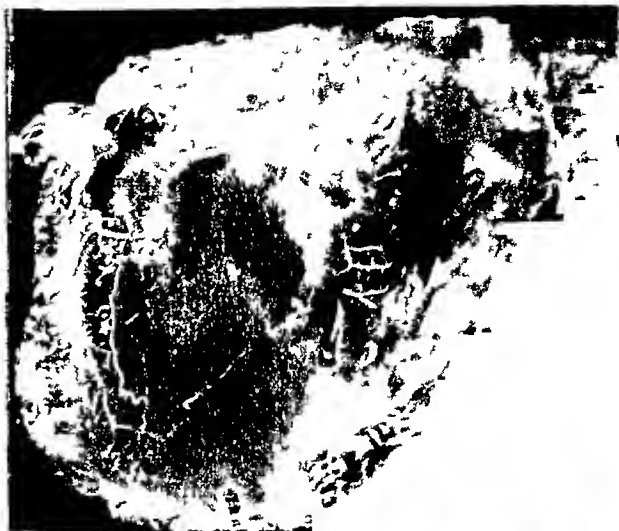
D Epicardium abraded, asbestos applied, pericardium grafted onto heart. Later on, descending coronary artery and right coronary artery were completely occluded by repeated operations. Several months later, specimen removed and circumflex artery was injected. Note filling of right and descending ramus of left coronary artery. Also note actual communications between coronary arteries and arteries of the pericardium.

These colored reproductions are necessarily reduced in size. It is suggested that they be observed through a magnifying glass.

5A



5B



5C



5D

FIG 5—In these specimens the epicardium was abraded, asbestos was applied and grafts were placed. Coronary arteries partially occluded at subsequent operations. Note intercoronary and extra coronary communications. (C) Had a graft of omentum and shows many blood vessels.

6A



6D

6C

FIG 6—Intercoronary communications produced by coronary artery occlusion. Upper left shows a circle of new vessels around the apex of the heart with all three coronary arteries communicating with each other. Note character of new vessels. In upper right, common left coronary artery above the septal branch was completely occluded. Note the new communication from the right to the left circumflex, posteriorly. (C) shows communications between the descending ramus of the left coronary artery and circumflex ramus of left coronary artery. (D) shows posterior aspect of the heart and a communication between circumflex branch of left coronary artery and the right coronary artery.



FIG 12 —Human heart Patient totally incapacitated Operation Patient improved and returned to work Death two years and three months later from cerebral hemorrhage Specimen injected through coronary arteries and cleared by Spalteholz method Note the vessels in the grafts which are more superficial than the deeper coronary vessels Clinical improvement can be explained by these extracoronary vessels

accomplishes a similar result. Ten years ago I studied a few inflammatory agents and found that some produced a very severe reaction, and concluded that it was dangerous to use certain substances. Comparative measurements of the effect of different inflammatory agents on the heart was carried out by Schildt, Stanton and myself¹ in the past three years. Other workers in the field have used different substances but ours is the only recorded attempt to measure this factor and to compare the effect produced by one substance with the effect produced by another substance. We studied the effect of more than twenty substances and found that one of the silicates in the form of powdered asbestos produced the most desirable result. Again, we observed that one cannot indiscriminately select the inflammatory agent to be used. Some are extremely dangerous. Dosage is also important. We found that 0.2 Gm. of powdered asbestos was safe, that it produced a highly vascular reaction between heart and surrounding tissues and that the reaction was not too severe. We also found that the reaction extended over a period of months. It was not of short duration.

We ligated the descending ramus of the left coronary artery at its origin in 19 dogs that had been treated previously with asbestos. Out of these, six died and 13 recovered. This was a mortality of 31 per cent, and can be compared to a mortality of 70 per cent in control experiments. Likewise, in these experiments we could demonstrate a reduction in the amount of myocardium destroyed following ligation of the artery as compared to the results in normal control experiments. Indeed, in a few experiments, the artery was ligated and an infarct did not develop. These experiments conclusively show that asbestos applied to the surface of the heart produces communications between the coronary arteries. Figure 5 shows specimens in which asbestos had been used.

B—CORONARY OCCLUSION PLUS A FACTOR OF TIME

This is another stimulus for the production of intercoronary communications. It is very effective in animals and it can be effective in patients. Those patients who make a good clinical recovery after coronary occlusion do so because they develop good intercoronary communications. If the heart can tolerate ligation of a coronary artery then in the course of a few weeks, good communications between the coronary arteries can be demonstrated. This is illustrated in Figure 5. It is to be noted that the factor of time is necessary for this stimulus to become effective. In other words, the animal, or the patient, must continue to live long enough for these channels to develop after the coronary occlusion. Occlusion, in the patient, is produced by the disease in the artery. It is not a step to be taken by the surgeon. Can the component of time be provided by surgical methods? The answer to this query is that surgical methods can contribute the time factor. It is provided by extracoronary communications and by the effect of inflammatory agents on the heart. By providing this time factor we can include this as a third concept or principle by which the circulation in the heart can be improved by operative methods (Fig. 6).

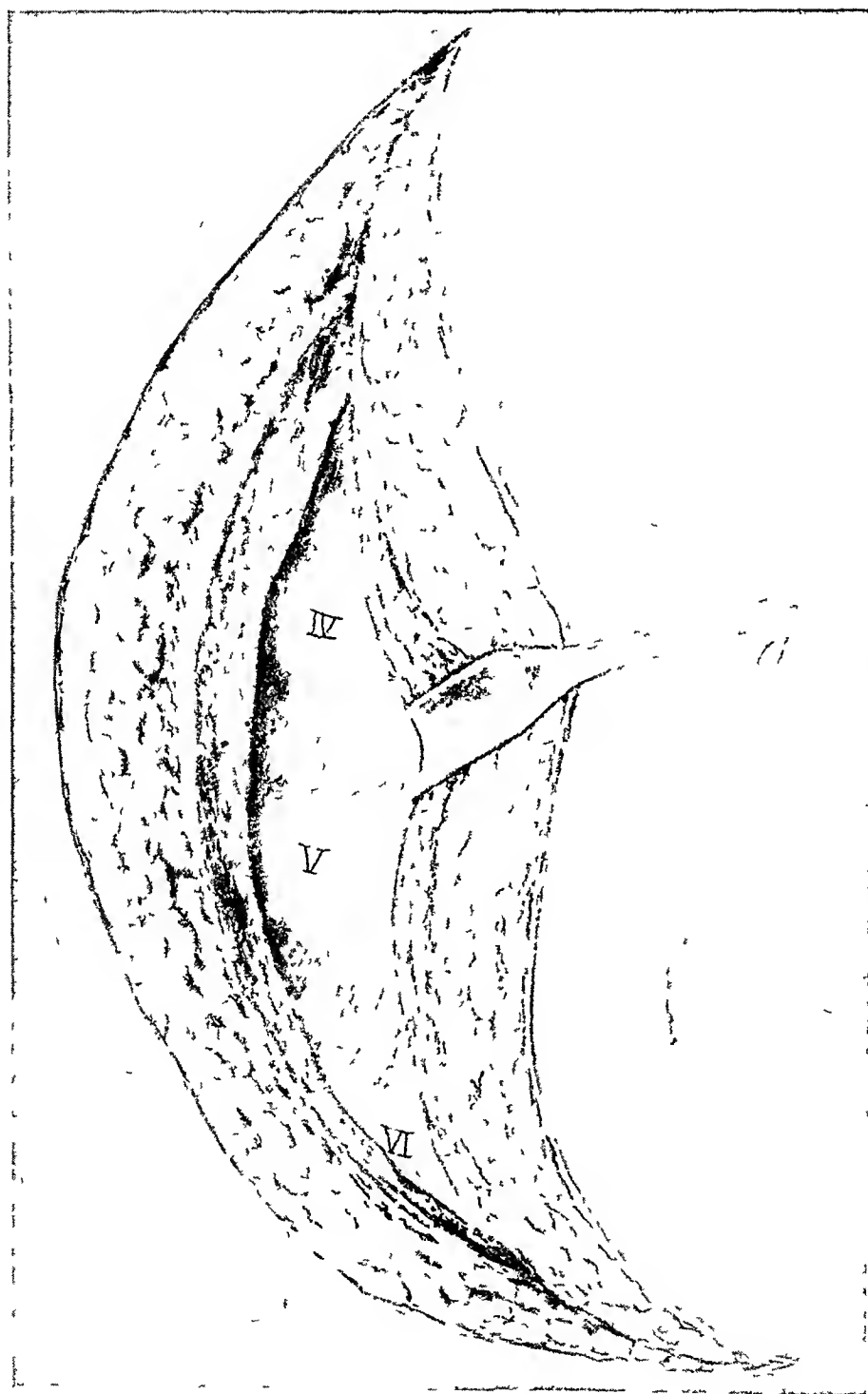


FIG 7—Skin incision over the precordium exposing the 3rd, 4th, 5th and 6th costal cartilages

This, in brief then, is the evidence to support the operative approach to the coronary problem. You will notice that it is all built upon experimental evidence. This is the only foundation upon which I should like to have it built.

The next step is a matter of applying these ideas and methods to patients with coronary artery disease. Let us be reasonable in our attitude towards this aspect of the problem. What kind of patient should we accept for operation? We know that we cannot give a new set of coronary arteries

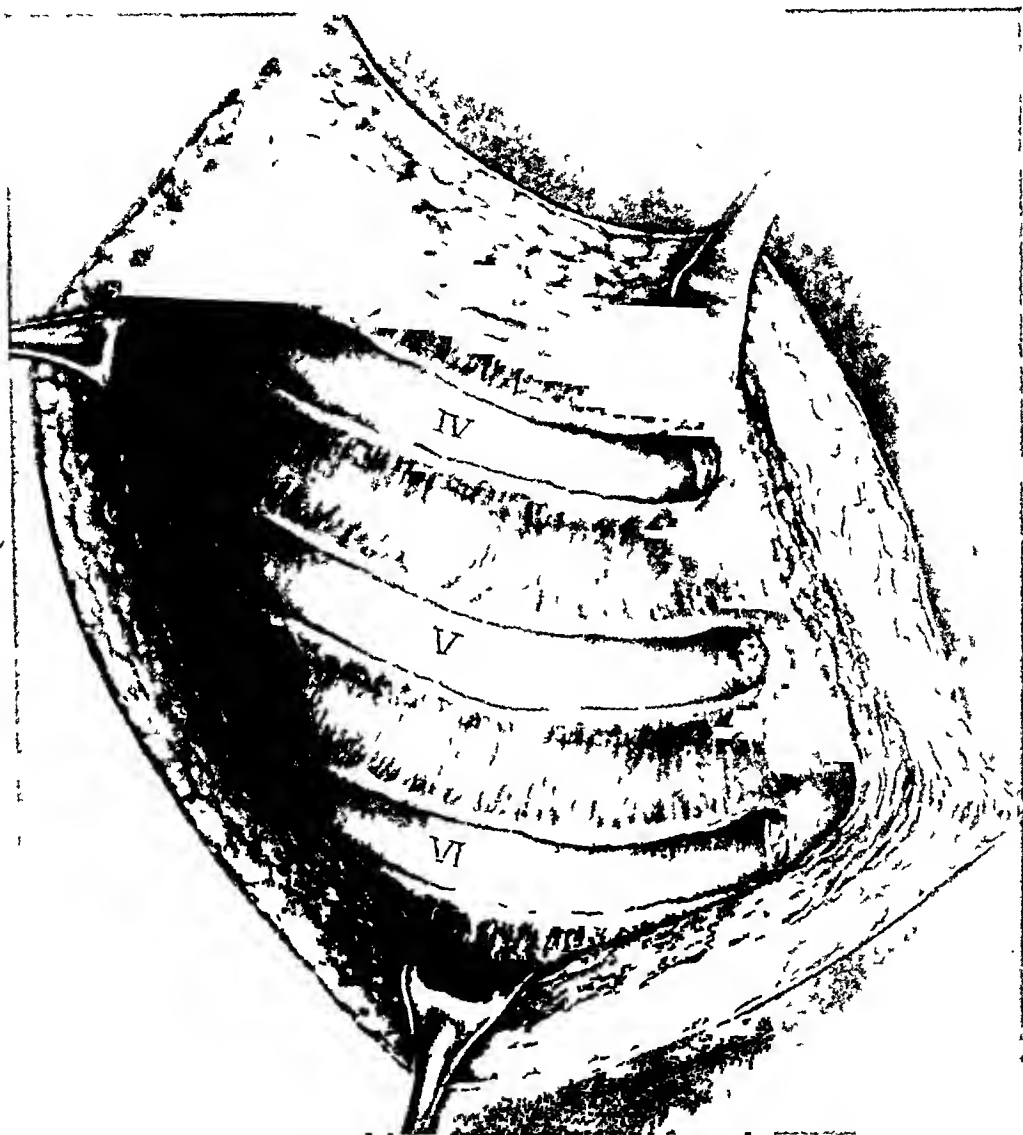


FIG 8—Pectoral muscle is retracted. Costal cartilages and ends of ribs removed.

to the heart. We know that we cannot give a new myocardium to the organ. It is clear to me, and I think it must be clear to you, that advanced disease is practically hopeless from the surgical point of view. Early disease with slight irreversible destruction of myocardium is the type of case for operation. The purpose of the operation is to give the heart something that will protect it when occlusion strikes, something that will keep the flame of life from going out. A concise presentation of this matter is given in Tables II and III.

TABLE II

Requirements for Operative Treatment.

- 1 Localized arterial and myocardial disease require a blood bath which can be provided by operation and which can prevent
 - a Infarct formation
 - b Ventricular fibrillation
- 2 Extensive arterial and myocardial disease require a new set of arteries and a new myocardium which cannot be provided by operation

TABLE III

Classification of Coronary Artery Disease

- 1 Trigger types with anoxic heart muscle which may produce ventricular fibrillation
 - a Threat to life
 - b Blood-bath to trigger area is prophylactic
 - c Types
 - (1) Patients with little or no destruction of myocardium
 - (a) Have the least risk
 - (b) Obtain the best result
 - (2) Patients with definite destruction of myocardium The amount of destruction determines
 - (a) Risk
 - (b) Result
- 2 Non trigger type with approaching myocardial failure
 - a Extensive destruction of myocardium
 - b Optimal period for operation has passed as concerns risk and result

PRESENT OPERATIVE TECHNIC

I prefer nitrous oxide anesthesia ⁴ We have no problem with anesthesia or with respiration. The anesthesia is light and when the operation is completed the patient becomes immediately conscious. The patient is placed in semi-Fowler's position on the operating table. The incision is curved along the left sternal border over the fourth, fifth and sixth costal cartilages and curved laterally along the sixth rib (Fig 7). The incision is carried through underlying muscle to the third rib and costal cartilages. The fourth, fifth and sixth costal cartilages are removed completely (Fig 8). A few centimeters of each of these ribs is also removed. The pleura is incised where these structures were removed and the pleural cavity is entered. The tissues between these incisions are left intact. The internal mammary artery is left intact. The inflation of the lungs is regulated so that the left lung comes well up with inspiration and collapses nicely with expiration. The pericardium is then sutured to the precordium in such a way that the heart will not be rotated from its normal position (Fig 9). The lining of the parietal pericardium everywhere is roughened by special burrs (Fig 10). Powdered asbestos, 0.2 Gm., is then applied to the heart. Some of this is rubbed into the parietal pericardium with a burr and some, mixed with saline, is dipped upon the heart and along the mammary artery and vein. Mediastinal fat is brought in through openings in the parietal pericardium so that it comes into contact with the heart. Fat is probably the best tissue for purposes of vascularization. All tissues that come into contact with the heart serve as grafts. The parietal pericardium is sutured to the chest wall (Fig 11) so that the heart and the precordium are in contact. The internal mammary artery and the intercostal arteries are in close proximity to the heart. It is advisable not to touch the heart any more than necessary. I do not

REVASCULARIZATION OF THE HEART

like to palpate the coronary arteries to see whether they are sclerotic, although I did this in some of the early operations. There may be some risk in doing this.

Closure is then carried out. The pectoral muscle is sutured where it was incised. An is removed by suction from the left pleural cavity. Subcutaneous sutures are placed. The skin is closed by suture. Drains

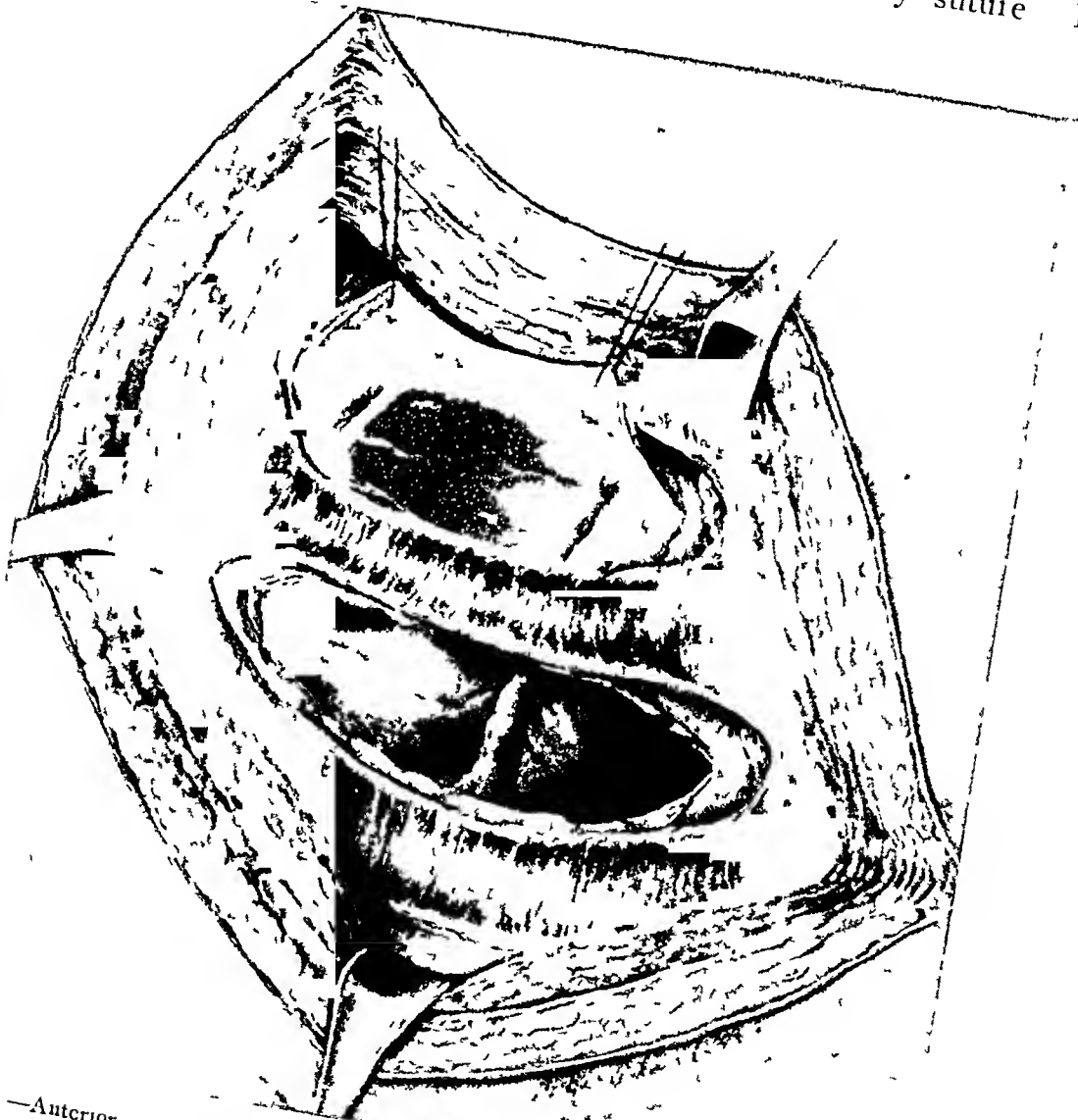


FIG 9—Anterior parietal pericardium opened bringing heart into direct contact with chest wall

The patient is placed in an oxygen tent. Fluid in quantities of three to five liters are given intravenously, daily. We feel that administration of ample fluids may be a factor in avoiding intravascular clotting. Muscle juices absorbed into the blood stream are conducive to postoperative thrombosis, and administration of a reasonable quantity of fluids may help to get rid of this factor. Quinidine is given before and after operation. A test dose of three grains, followed by five grains, is given the night before the operation. An additional dose of five grains is given in the morning before operation. Morphine is given as necessary.

Usually fluid does not collect in the left pleural cavity. If it does form, it can be left to absorb or it can be removed by aspiration.

The operation has undergone several changes since we first carried it out. Originally I used pedicle grafts from the chest wall. I also carried out a bilateral approach in several patients, going in on each side of the sternum. It was my desire to place grafts upon as much of the heart's surface as possible.

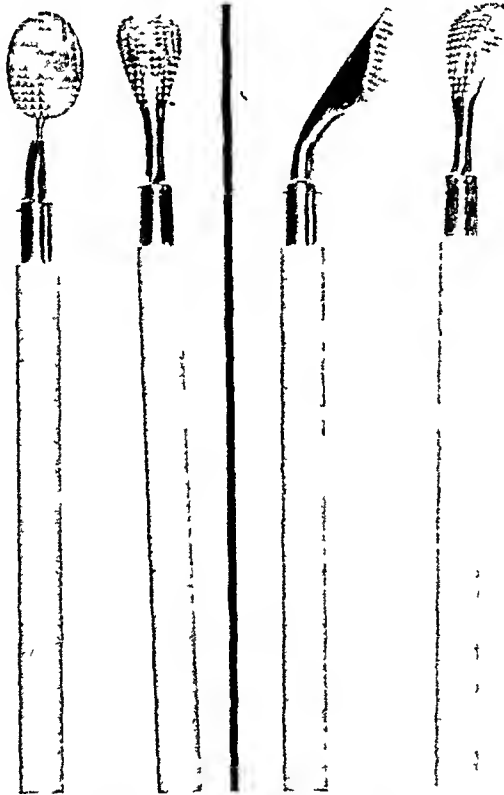


FIG 10—Special burs for abrading parietal pericardium

The operation as outlined above is a procedure of small magnitude. The removal of the bony precordium allows the chest wall, with the mammary artery and intercostal arteries, to come into contact with the heart. Perhaps in the future, a method might be worked out by which an inflammatory agent can be injected into the pericardial cavity and become effective by sealing parietal pericardium and mediastinal fat to the heart. In one of my patients who was in circulatory failure, I removed a costal cartilage under novocain anesthesia and simply introduced an inflammatory agent into the pericardial cavity.

RESULTS OF OPERATION

When it comes to making an evaluation of the operation, one encounters several problems. The most important problem is to determine whether the improvement noted by the patient is due to the operation or whether it would have occurred in the natural course of the disease without operation. We know that the natural course of the disease varies from that of im-

minent death to that of almost full clinical recovery over a period of years I can think of one or two methods which may help to stabilize interpretation of this variable factor. One method is by the selection of patients whose clinical course is either horizontal or declining over a period of several months. The patient becomes his own control for evaluation of his status before and after operation. When the clinical course has become



FIG. 11—Pericardial pericardium sutured to chest wall by about ten sutures. Powdered asbestos, 0.2 Gm., placed on the surface of the heart and also over the tissues in contact with the heart.

more or less stabilized we can interpret improvement in the clinical course as having been produced by the operation. However, we cannot be absolutely secure in this deduction. It is still possible that the improvement might have occurred without the operation. Another method by which the result of the operation can be determined is to get what we might call a group experience. If each patient in the group followed a pattern after operation, the evaluation would be more simple. But we must allow for variables in the group. The occlusive nature of the disease may be progressive or it

may be quiescent for a time and then become progressive. It is also possible to have patients in the group who have extensive and irreversible disease of the arteries and myocardium. Such patients, even though they are fortunate enough to survive, may get little or no improvement from the operation. Such patients belong to an inoperable group, but it is almost impossible to recognize them clinically so as to avoid operating upon them. It might also appear to be possible to evaluate results of operation by having two groups of patients going along side-by-side: one group with the operation and the other group without the operation. We could compare clinical results including pain, exercise tolerance, duration of life, etc. Such data would be valuable, but at the same time we must recognize the fact that it is impossible to get two identical groups of patients. It seems to me that the best way to get measurements on the effectiveness of the operation is to take patients whose clinical course has become stabilized and let each patient become his own control. *It is possible for us to err in either direction by making evaluations that are not justified and by refusing to make evaluations that are justified. One mistake is quite as serious as the other.*

There are two considerations that come to our aid in the evaluations of results. One is the knowledge gained by experimental work, the other is the information gained by examination of the heart after the patient dies, and interpretation of the clinical result in terms of the specimen. Without these aids I should almost refuse to make a clinical interpretation of result. This conservative point of view I believe is necessary until the operation becomes established as a recognized form of treatment. To illustrate this attitude I might mention the fact that some patients stated that they felt better as early as one week after operation. Lichy and I had no explanation for this early improvement from the laboratory, and we refused to place any significance in these statements of improvement. Later we found in the laboratory that intercoronary communications were demonstrated as early as five days after operation and with this as an aid we are now willing to accept early improvement as being significant. Likewise, we have had the opportunity of interpreting the clinical course in terms of the specimen after death of the patient. One of these patients was able to work as a salesman after operation. He felt much better. Two years and three months after operation he died from a cerebral hemorrhage. Examination of the heart showed a number of vascular communications between the heart and the grafts (Fig. 12). The cleared specimen is very significant in that, in my estimation, it can account for the clinical improvement of the patient. This is the best proof that I can give that coronary artery disease can be helped by operative methods.

I think the patient is able to make an accurate appraisal of the results of the operation. It is the patient who feels the pain and who knows whether his ability to get around has been improved. Appended are statements from

some of the patients made within the past few months concerning their present status

"Feeling fine and able to work hard every day" (Operation 2-13-35)

"My condition is very good considering everything. The heart is going along well and I believe I may live for several years, if some other trouble does not take me out of circulation" (Operation 7-9-35)

"I have had seven years of borrowed life due to your wonderful skill and loyal interest in my case. I am working every day" (Operation 2-22-36)

"I do a hard day's work in the machine shop everyday. I haven't missed a day's work for a long time. I feel fine and have no trouble" (Operation 11-18-36)

"I am still coming along in great shape and feel equal to about any occasion. I am well pleased with my condition. Feeling fine and able to work" (Operation 12-3-36)

"The angina pain bothers me after meals, exertion and excitement, very seldom at rest. I feel, however, that I have been greatly helped by the operation" (Operation 1-30-37)

"At present, and for the past three years, I have been working as a chef. I work very hard but feel no ill effects from it. I use absolutely no medication of any kind and I am not under any medical care" (Operation 1-30-37)

"I feel fine. I have no trouble with my heart" (Operation 3-6-37)

"I have been feeling fine, eat anything and everything, and as much as I want, without distress. I walk up and down stairs, get on and off street cars before they stop *etc.*, with no discomfort. I go to the stock market every day, which is equivalent to work, and it does not affect me. I feel sure that the operation saved my life and I expect many more years of continued good health. Most of the time I don't know I have a heart—going great!" (Operation 4-24-37)

"I was a principal in the Public Schools before I developed this condition and became totally incapacitated. I was confined to my room for a year and could walk no farther than from the bedroom to the bathroom without pain. I experienced early benefit from the operation, and at present, am feeling well, enjoying life and able to do a moderate amount of work" (Operation 7-30-37)

"In Florida since November 1, 1942, and expect to remain here until May 1, when I expect to return to work. Am much better—nerves, heart action and frequency and severity of spasms much improved and I expect to continue to improve" (Operation 8-4-37)

"In general, pain since operation is about one-quarter its previous frequency and severity" (Operation 8-13-37)

"I have gained much strength since the operation and find I do not tire nearly as easily as before. I have no pain around the heart. I have none of the old symptoms since the operation. I feel that I have been fortunate in having the operation made available to me. I have not yet returned to work, following the advice of Doctor Beck at the time of operation, to the effect that I should wait about six months thereafter before attempting to work. This period will not be up until about May 1st" (Operation 10-30-42)

"I do feel improved over that of a few weeks ago. I would say that, offhand, I feel about 75 per cent of what I felt preoperatively. I expect to improve steadily though—and realize it takes time. I walk around, drive a car and do mild recreational exercises" (Operation 1-17-43)

Other Investigations—O'Shaughnessy⁵ was the first to take up the work of revascularization of the heart after we had begun our studies. He used omentum for his grafts and brought it through an opening in the diaphragm and applied it to the apical region of the ventricles. After per-

forming experiments upon animals he applied the procedure to patients, beginning in January, 1936. He claimed originality for the idea of cardio-omentopexy, as he called it, although Tichy and I used omentum in our experimental work beginning in 1932. Herniations developed in several of our experiments and we did not apply this procedure to patients. O'Shaughnessy demonstrated one specimen, from a dog, in which barium was injected into the vessels of the graft and it appeared in the coronary arteries. This was confirmation of work that we had done. He also presented microscopic evidence of blood vessels in the grafts, but such communications have no significance relative to the amount of blood that might be going across such adhesions. His experimental evidence, by itself, can scarcely be regarded as convincing evidence that the operation should be undertaken upon patients. The results with the patients were reported by him as beneficial.

W. F. Rienhoff, Jr.,⁶ of the Johns Hopkins Hospital, in a discussion of this work stated as follows: "Independently, and without any knowledge of Doctor Beck's experiments, or interest in this problem, we began, in October, 1934, investigating different methods of supporting an interrupted coronary circulation. We have used a series of old dogs for the reason that the independent development of a collateral circulation in younger animals is so readily achieved that recovery from ligation of the right or left anterior descending coronary artery may be clinically uneventful and easily survived by the animal. Doctor Beck did not state whether his series of dogs were young or old. In a small series of nine dogs, the epicardium was then moistened with half strength iodine and the omentum wrapped, so to speak, completely around the heart, entirely covering the anterior surface. Three to six weeks later, ligation of the entire left coronary artery just below its origin from the aorta and above the division into the left anterior descending and circumflex arteries was accomplished by taking a deep bite with a No. 2 French needle in the ventricular wall in the region of the left coronary artery just beneath the tip of the left auricle. The distension of the coronary veins distal to the ligature proved its location. No disturbance in cardiac rhythm followed these ligations after previously performed cardio-omentopexy, either clinically or in the electrocardiogram. The dogs were not at all ill. Whereas, before similar ligation was invariably fatal, not one animal succumbed after adhesion of the omentum to the heart had been produced. These specimens will be reported on later."

I have the following comment to make about this discussion. We have never found any difference in the coronary bed in dogs, whether the dogs are young or old. In the normal heart the coronary arteries are essentially end-arteries, regardless of the age of the dog. There are certain slight variations in intercoronary communications that are present in a group of specimens but these variations, slight as they are, are the same regardless

of age. My associates and I have not found age to be a factor in mortality after coronary artery ligation. I found tincture of iodine to be a strong necrotizing agent and too dangerous to use. There is no coronary vein in the location of the common left coronary artery. The vein is several millimeters below the bifurcation of this artery. If the artery is ligated, the vein is not ligated by the same suture, if the vein is ligated the artery is missed in this suture. We have never been able to ligate the common left coronary artery in one step, with recovery, regardless of the method used for protection of the heart before this was done. On the basis of our experience, I do not believe this can be accomplished in one stage. It is difficult to accomplish complete occlusion of this artery by repeated steps. We have accomplished this a number of times and it requires considerable care not to take the artery down abruptly in any one operation, thereby producing death of the animal. It also requires weeks or months between operations for intercoronary channels to develop so that an additional step in the occlusive process can be tolerated. There is no reference in the Quarterly Cumulative Index Medicus to a subsequent report of these experiments by Rienhoff.

Burchell⁷ carried out experiments in which grafts were placed upon the heart and the coronary arteries were occluded. A quotation from his work is as follows: "So far as these studies on coronary occlusion in dogs are concerned, the rôle played by vascular channels in pericardial adhesions in supplying blood to the myocardium has been minimal or nonexistent. The possibility that the small vascular connections, between a graft and the heart might develop to a functioning value cannot be denied, but in the experiments seemingly favorable to such a result it has not occurred." In making this analysis of his own experimental work, Burchell was not urged by a desire for independent accomplishment. He was critical throughout, and, I think, he was essentially correct. However, I think if he had gone farther with his experimental effort he, no doubt, would have demonstrated anastomoses such as are illustrated in the present communication.

Heinbecker and Barton⁸ carried out experiments in which a mixture of gelatin, aleuronat, starch, glycerin, water and lionite was introduced into the pericardial cavity. In some experiments these authors also used sodium morrhuate. After these substances were introduced the pericardium was closed and then the pericardium was sutured to the retrosternal tissues. Fourteen animals were prepared in this manner. Four to 12 weeks later these animals were again operated upon and the descending ramus and the circumflex ramus of the left coronary artery were ligated about one centimeter from the aorta. Eight of the 14 animals died and six survived. Infarcts were not found in these specimens.

We carried out experiments in which we tried to repeat this procedure. We were not able to get any animals to survive ligation of both of these arteries in one step. It would be highly desirable if Heinbecker and Barton

would repeat these experiments and inject the coronary arteries and clear the specimens. These ligations are very much greater than anything that any of my associates or myself have been able to accomplish.

Thompson and Raisbeck⁹ carried out experiments in which talc was introduced into the pericardial cavity and they applied this procedure to patients with coronary artery disease. These authors found that the mortality following coronary artery occlusion was reduced by the use of the talc. They found that ligation of the descending ramus of the left coronary artery and vein at a point one centimeter below the origin of this artery carried a mortality of 50 per cent. A similar ligation was performed, but, in addition, talc was introduced into the pericardial sac at and around the site of ligation. Here the mortality was 25 per cent. In another group of experiments talc was introduced and two or three weeks later, a similar ligation of the artery was done—there was no mortality.

We studied the effect of talc, and repeated these experiments. We were not able to obtain the same beneficial results as these authors reported. We also found that powdered asbestos produced a much more vascular type of reaction than did talc.³

Reference should be made to the work on coronary vein ligation. Ligation of corresponding vein and artery, as compared to ligation of artery alone, is a subject that has received much study by surgeons. These studies concerned the femoral artery and vein and also the vessels to the upper extremity. Gross, Blum and Silverman¹⁰ applied the idea of vein ligation to the heart. They ligated the coronary sinus and found that this procedure was beneficial, in that the amount of muscle destroyed following arterial occlusion was less in extent when artery and vein were ligated as compared to results when artery alone was ligated. These authors did not find that vein ligation reduced mortality of arterial ligation. However, Fauteux¹¹ found that if he ligated the magna cordis vein and then ligated the descending ramus of the left coronary artery that the mortality was very much less than if he ligated only the artery. Beck and Mako¹² studied this subject and found that in the experiments in which the artery was completely occluded there was no definite difference in the size of the infarct whether the vein was or was not occluded. This did not seem to be the case when the artery was only partially occluded instead of completely occluded. In these experiments it appeared that ligation of the vein did reduce the size of the infarct as compared to the infarct following partial occlusion of the artery alone. Mako and I concluded that the beneficial effect following vein ligation was probably not great enough to justify application to patients. We could not obtain the good results reported by Fauteux. Recently Fauteux reported an operation upon a patient with sclerosis of the descending ramus of the left coronary artery in which he ligated the magna cordis vein. The physiology of this subject has been studied by Gregg, and his associates, in Wigger's laboratory.¹

The query might be raised as to why certain investigators were able to accomplish so much in the way of coronary artery ligation. I believe a partial answer can be given to this query. One explanation concerns the site of the ligation. If this varies in different experiments the results will vary, because one or two arterial branches may be missed in some experiments if they come off proximal to the ligation, and these branches make a difference in the result. Another explanation lies in the method of producing the ligation. A suture placed in the region of the artery without dissection of the artery may well miss the artery, as I think must have been the case with Rienhoff. He used the location of the magna cordis vein, and the distension of this vein, to tell him whether the artery was occluded, and he did not report on the facts as found in postmortem examination of the specimens. Another explanation, no doubt, is related to the natural enthusiasm and desire for accomplishment on the part of the investigator. This may be a real factor, especially in the early developmental period, after we did our first experiments. It is so easy to over shoot the mark! Of course, the reader must remember that without enthusiasm none of this experimental work would have been undertaken. I would gladly welcome the accomplishments as set forth in some of the reports. My associates and I have tried over and over again to improve the preparation of the heart so that it could tolerate occlusion of the descending ramus of the left coronary artery and the circumflex branch of the left coronary artery in one step. If the heart could be so prepared then, indeed, we would have a very good method for the treatment of coronary artery disease in patients. We can accomplish something in the way of arterial ligation but it is not that much. No doubt the methods for preparation of the heart can and will be improved by future experimentation.

SUMMARY AND CONCLUSIONS

- 1 The surgical approach to the treatment of coronary artery sclerosis has been established upon a scientific basis. Coronary artery disease is compared to epilepsy. The trigger in the heart "fires" or discharges and produces a state of incoordinated contractions and relaxations of the heart muscle fibers. This is the well known "heart attack" and is fatal. A small amount of blood to the zone of anoxemia can prevent the trigger from "firing." This may be regarded as a blood-bath and can be produced by operative methods.

- 2 A study group of 30 patients with coronary artery disease were operated upon. The patients who recovered from the operation were partially or completely relieved of pain. Their ability to get around has been increased, some of the patients are doing hard physical work.

- 3 The operation can be considered as a procedure in therapy.

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CLINICAL APPRAISAL OF THE BECK OPERATION*

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THE NATURAL HISTORY OF PATIENTS with coronary sclerosis, with and without myocardial infarction, varies greatly, but the average life expectancy is brief. In Table I are compiled the average duration of life after the onset of symptoms as determined by several observers.

TABLE I

Observer	Number of Patients	Average Duration of Life after Onset of Symptoms (In Years)
MacKenzie ¹ (angina pectoris)	213	5 4
White and Bland ² (angina pectoris)	213 patients dead	4 4
	273 patients living	5 1
	486 total	4 9
(coronary thrombosis)	101 patients dead	1 5
	94 patients living	2 4
Wedd and Smith ³ (angina pectoris)	166 patients	5 8
Levine ⁴ (coronary thrombosis)	101 patients dead	3 4
	271 patients living	2 3
Feil ⁵ (angina pectoris)	100 patients (private)	4 5
(coronary thrombosis)	256 patients dead	
Lakeside Hospital	Autopsy performed	1 1 (See Fig 1)

In Figure 1, 256 cases of myocardial infarction are tabulated according to the duration of life from the onset of symptoms. These patients received conventional medical treatment but medical treatment is, at best, palliative. Medical therapy does not in any way alter either the underlying pathologic changes in the coronary arteries nor does it stay the progress of these changes. The surgical approach of attempting to improve the coronary artery circulation is fundamental. Knowing the grave prognosis of patients suffering from coronary artery sclerosis, the operation of Beck's was a welcome addition to therapy. Beck's operation, described in previous papers,⁶ consists, essentially, of increasing coronary circulation by producing inflammation on the surface of the heart and implanting grafts upon the heart. Thirty-seven patients comprise the basis of this paper. Two previous reports on some of these patients have been made.^{7, 8}

Types of Patients Selected for the Operation—The first patients who were operated upon were for the most part suffering angina on slight exertion. Because of the serious coronary disease and the associated pathologic changes (generalized arteriosclerosis, myocardial fibrosis) the operative

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mortality was high. As the operative technic was further improved, patients were selected with less severe coronary disease and without complicating factors. The diagnosis of coronary artery disease was definitely established and other pathologic conditions simulating the symptoms of angina were ruled out. Hypertension was not alone a contraindication. Diabetes, if present, was under control. The age of the patient was an important factor in selection—the younger the patient, the more favorable the outcome, although one of the best results of the series (Case 20) was 70 years of age. Pulmonary

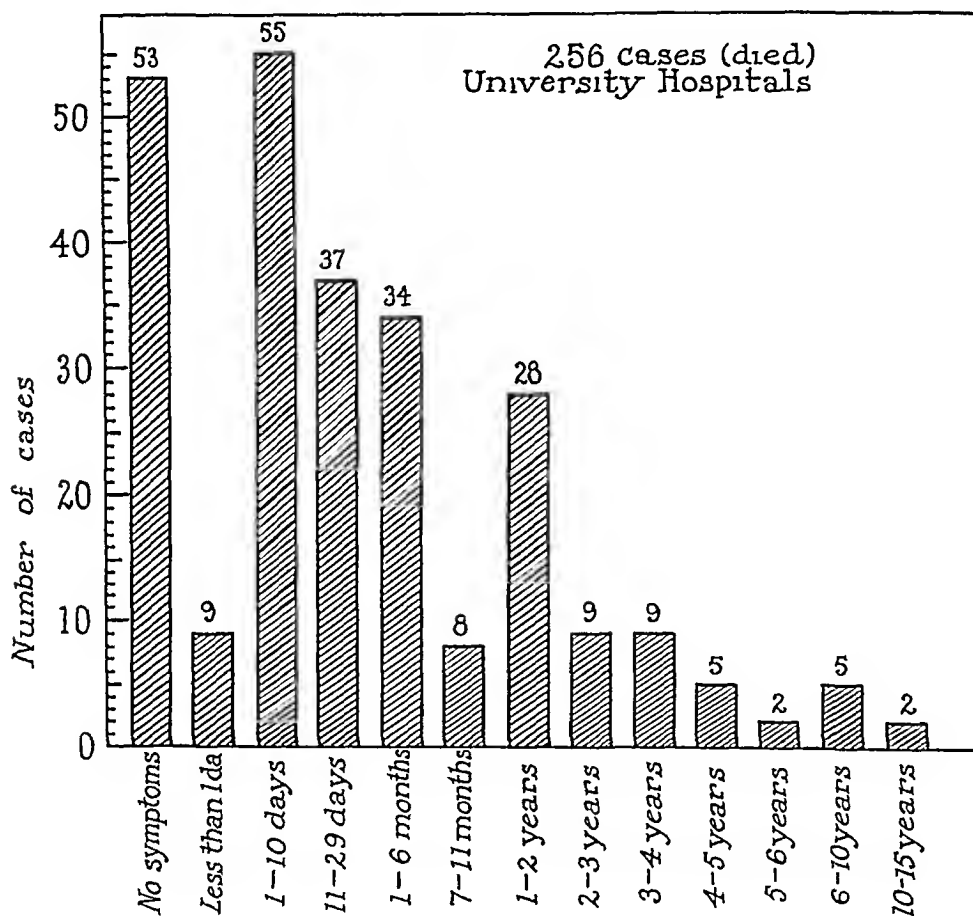


FIG. 1.—Tabulation of 256 cases of myocardial infarction, according to the duration of life from the onset of symptoms

disease (severe emphysema, chronic bronchitis, bronchiectasis) was of course a contraindication. Obesity increased the operative hazard, although some of the successful cases were overweight.

Postoperative Course of Patients Twenty-three patients (62.2 per cent) survived the operation and have been followed. Fourteen patients are still alive of whom nine are in excellent condition and five are in good condition, not completely relieved of symptoms but who have increased exercise tolerance (Table II).

APPRAISAL OF THE BECK OPERATION

TABLE II—JULY 1 1943

Case	Age	Survival Period		Living	Dead	Condition After Operation
		Years	Months			
1	56	8	5	+		Excellent†
3	55	2	6		+	No improvement
4	57	8	0	+		Good†
6	61	6	1		+	Excellent
9	51	5	8		+	Excellent
11	49	7	4	+		Excellent
13	58		6		+	No improvement
15	54	6	0		+	Excellent
17	56	6	7	+		Excellent
18	55	5	1		+	Excellent
19	55	6	7	+		Excellent
20	70	2	5		+	Excellent
21	57	6	5	+		Good
22	48	6	5	+		Excellent
23	55	6	4	+		Good
24	47	1	5		+	Little improvement
25	57	6	2	+		Excellent
26	56	5	11	+		Excellent
27	53	5	11	+		Excellent
28	55	5	10	+		Good
31	54		4		+	No improvement
36	59		9	+		Excellent
37	35		6	+		Good

*Excellent Sufficient improvement to permit patient to return to his former occupation with no or minimal symptoms

†Good An increase in exercise tolerance and diminution in symptoms

SUMMARY OF PATIENTS NOW LIVING

Case 1—Arteriosclerotic heart disease and angina pectoris of nine years' duration, severe for five years, moderate generalized arteriosclerosis with hypertension, arterial pressure 169/92. Moderate chronic pulmonary emphysema. A 48-year-old farmer, with gradually diminishing exercise tolerance, finally became incapacitated for any work because of retrosternal pain, fatigue and dyspnea. Operation was performed February 13, 1935. Four months later he began to do light work around the hospital as a gardener and made 82 trips on the steps without pain, stopping because of dyspnea. It is now eight years and five months since the operation and he is able to work 12 hours daily as a farmer. He feels no more than the usual fatigue at the end of the day. The result in this, the first patient to have the operation, is excellent.

Case 4—Arteriosclerotic heart disease, coronary sclerosis and angina pectoris of four and one-half years' duration, generalized arteriosclerosis and diabetes mellitus. A surgeon, age 50, with angina of effort and emotion, was totally incapacitated in December, 1932. Subtotal thyroidectomy was performed in January, 1933. He had a coronary thrombosis in February, 1933. The patient had had diabetes mellitus since 1918, requiring insulin. He had had pain in the legs for three years on walking. A roentgenogram of the legs showed calcification of the vessels. The electrocardiogram showed a deep Q₃. Operation was performed July 9, 1935. The exercise tolerance increased from 18 trips before operation to 32 trips after operation. The patient has less pain on exertion and exposure to emotional stress. The results in this case are classified as good.

Case 11—Arteriosclerotic heart disease and angina pectoris for 11 months, probably coronary thrombosis at onset of illness. A tailor, age 42, had angina of effort and emotion. He became totally incapacitated. Rest and drugs failed to do more than give

relief Angina was produced by 24 trips on the steps After glyceryl trinitrate he was able to make 42 trips before angina occurred The limb-lead electrocardiogram was normal but the T wave in Lead 4R was negative Operation was performed February 22, 1936 The patient is now able to work He can tolerate 97 trips on the steps and stops because of dyspnea and not because of pain The result in this case is excellent

Case 17—Arteriosclerotic heart disease and angina pectoris, myxedema and secondary anemia A machinist, age 50, had had a typical history of angina of effort for 18 months The basal metabolic rate was -30 and the patient took small doses of thyroid The electrocardiogram revealed left axis deviation and QRS of normal voltage, the T wave was almost iso-electric in all leads, including the chest lead Operation was performed November 18, 1936 Congestive heart failure developed after operation and cleared up with appropriate treatment Tolerance for exercise increased from 36 trips on the stairs before operation to 50 trips after operation The dose of thyroid extract has been increased to $\frac{1}{4}$ grain He does not take any nitroglycerin He is working at his job as machinist It is now six years and seven months since the operation was done The result is excellent

Case 19—Arteriosclerotic heart disease and angina pectoris of 17 months' duration A coal miner, age 49, was totally incapacitated during the entire course of his illness He had severe pain at rest and morphine was given for the pain Theophylline with ethylendiamine and glyceryl trinitrate gave no relief The electrocardiogram showed alterations indicative of a remote posterior and basal infarct Operation was performed December 3, 1936 Marked improvement followed operation He is able to do much work on his farm It is now six years and seven months since the operation and the result is excellent

Case 21—Arteriosclerotic heart disease and angina pectoris of five years' duration, mild diabetes mellitus A clerk, aged 51, failed to benefit from medical treatment, paravertebral injection with alcohol failed to give relief and he became totally incapacitated for work The left ventricle was slightly enlarged The peripheral arteries were calcified The electrocardiogram was normal at rest but after exercise showed definite alterations from normal Operation was performed January 20, 1937 The patient was much improved following operation The pain did not completely disappear but became less severe He returned to work but was forced to retire because of parkinsonism

Case 22—Arteriosclerotic heart disease and angina pectoris, thromboangitis A cook, age 42, had angina of effort and emotion for five and one-half years and was incapacitated for his work for two years He took morphine for the pain The left foot was cool, and the arterial pulse was not palpable in the left leg The electrocardiogram showed no significant changes before or after exercise Operation was performed January 30, 1936 He had several angina attacks in the early postoperative period Later he showed striking improvement He is at work as a chef and does not require medication The result is excellent

Case 23—Arteriosclerotic heart disease and angina pectoris of six months' duration A molder, age 49, had a typical history of angina of effort for six months and had to give up work for four months before admission Medical care with a long rest in bed did not increase his tolerance for exercise The anginal syndrome was produced by 53 trips, and after glyceryl trinitrate he was able to make 90 trips Electrocardiographic changes were present during the induced angina The circulation time was 20 seconds, Operation was performed March 6, 1937 The patient states that he has felt better since the operation and he is able to make 52 trips on the steps, stopping because of

moderate dyspnea. He works in his garden and does much physical work about the house without symptoms. We regard his results as good.

Case 25—Arteriosclerotic heart disease and angina pectoris of nine years' duration. A retired salesman, age 52, had some attacks which were sufficiently severe to have been caused by coronary thrombosis. The conventional electrocardiogram was normal, but the T wave in the chest lead was reversed in direction. The record taken during the induced anginal attacks after exercise showed changes suggesting a posterior and basal infarct. Operation was performed April 24, 1937. The patient states that there is definite improvement and that he is able to carry on his work, without symptoms. The result in this case is excellent.

Case 26—Arteriosclerotic heart disease and angina pectoris for one and one-half years, an attack of myocardial infarction one year before operation. A female school principal, age 50, had severe angina of effort and of emotion which totally incapacitated her. She was able to make but three two-step trips, stopping because of typical angina. Operation was performed July 30, 1937. Her convalescence was slow, but on October 11, 1937, she was able to make 12 trips, and on November 29, 1937, this was increased to 20 trips. In the intervening period, the patient has been able to walk a few blocks without pain. The result in this case is excellent.

Case 27—Arteriosclerotic heart disease and angina pectoris following an attack of coronary thrombosis two years previously. A factory superintendent, age 48, had angina of effort which caused him much distress. He was operated upon August 4, 1937, and his convalescence was uneventful. He left the hospital in 37 days. He was able to return to his job, working five to eight hours a day. The result is excellent.

Case 28—Arteriosclerotic heart disease and angina pectoris of six years' duration. A salesman, age 50, was unable to carry on with his work, and he was operated upon August 13, 1937, making an uneventful convalescence. He gradually improved and finally was able to do moderate exercise without pain. He has shown definite improvement. We regard the result in this case as good.

Case 36—Arteriosclerotic heart disease with angina pectoris. A male, age 39, a railroad dispatcher, had typical angina of effort for nine months. He was put to bed for four months but continued to have symptoms on effort. Blood pressure 106/74. The electrocardiogram showed right bundle branch block and an absence of a positive deflection in all "V" chest leads, 1-5. There was positive deflection in V₆. T was inverted in V_{3,4,5}. The record suggested old anterior and apical infarction as well as septal infarction. He is now able to walk several miles at a brisk rate without symptoms. He has returned to work. His electrocardiogram is unchanged. It is now nine months since the operation and the result is excellent.

Case 37—Arteriosclerotic heart disease with angina pectoris, rheumatic heart disease, mitral valvulitis with insufficiency. A male, age 35, physician, had angina of effort and of emotion for two and one-half years. This pain followed an episode diagnosed as coronary thrombosis although there was no electrocardiographic evidence. The heart was normal in size, but there was a moderately loud systolic murmur at the apex. This murmur had been detected for many years. Blood pressure 132/94. The chest lead in the electrocardiogram showed inversion of T after exercise. He was operated upon January 17, 1943, and made an uneventful convalescence. He has returned to his practice. It is now six months since the operation and he has less pain. He feels that the operation has given him definite improvement. The result is classified as good although the time has been too short to make a definite appraisal.

PATIENTS WHO WERE OPERATED UPON AND HAVE SINCE DIED

Case 3—An executive who after operation showed some improvement but continued to have pain

Case 6—A mechanic with severe generalized arteriosclerosis. He was much improved after operation and was able to work. He had some recurrence of his angina but lived six years and one month after operation.

Case 9—A painter who lived five years and eight months after operation. He was greatly improved and was able to return to work, working up to the time of his death.

Case 13—A bookkeeper who had left ventricular failure previous to operation. He did not improve and died six months later of coronary failure.

Case 15—A manager of a store who was very greatly improved by operation. He continued to have some angina of effort. He continued to work and died six years later.

Case 18—A cook who was greatly improved and returned to his work. He died five years and one month after operation of acute coronary insufficiency.

Case 20—A book agent, the oldest of the series, improved after operation sufficiently to return to his work. He died two years and six months after operation of cerebral hemorrhage.

Case 24—A tailor, who, after operation, continued to have angina and showed little improvement. He died one year and three months after operation of coronary thrombosis.

Case 31—This patient showed no improvement after operation, and died four months later of acute coronary insufficiency.

Operative Mortality—There were 14 operative deaths, or 37.8 per cent (Table III)

TABLE III

Case	Age	Days Lived	Cause of Death
2	53	6	Thrombosis of abdominal aorta
5	58	2	Mediastinitis (<i>C. welchii</i> infection)
7	57	4	Cerebral hemorrhage, bronchopneumonia
8	53	1	Coronary thrombosis
10	56	2	Coronary insufficiency acute
12	54	9	Bronchopneumonia
14	53	5	Bronchopneumonia
16	57	1	Coronary insufficiency acute
29	50	2	Bronchopneumonia
30	54	0	Coronary insufficiency acute
32	58	0	Coronary insufficiency acute
33	44	12	Coronary insufficiency acute
34	56	2	Bronchopneumonia
35	64	2	Coronary insufficiency acute

CASE WITH SEVERE CORONARY ARTERY DISEASE AND RECENT AND REMOTE MYOCARDIAL INFARCTION

Case 33—Male, age 44, had angina of effort for ten years. His pain had increased greatly during the six months before operation. One and one-half hours after operation he had an attack of severe retrosternal pain, with dyspnea. He was given morphine and papaverine intravenously and atropine sulfate hypodermically. His symptoms gradually subsided in 24 hours. His convalescence was satisfactory until the seventh postoperative

APPRAISAL OF THE BECK OPERATION

day, when he had severe inspiratory pain in the right chest. Later a pleural friction was heard. Thirty-six hours later another episode of pulmonary infarction occurred. On the tenth, eleventh and twelfth postoperative days he had severe retrosternal pain, dying on the twelfth postoperative day. The limb electrocardiograms showed elevation of R-T in all leads. No chest leads were taken after operation. The electrocardiogram taken a few hours before death showed typical changes of an acute *cor pulmonale*.

Autopsy—The postmortem examination revealed subintermural hemorrhage in the wall of the main left coronary artery and recent thrombosis of the ramus descendans left. There was recent infarction of the entire I-V septum. Remote thrombosis of the right coronary artery was found with remote infarction of the midlateral portion of the left ventricle. There were mural thrombi in the right auricle and in the apex of the left ventricle. Thrombi were also found in the branch of the right pulmonary artery to the right lower lobe. There was a recent infarct of the left kidney.

This patient illustrates the difficulties involved as the result of widespread coronary artery disease and the additional complications of pulmonary infarction and myocardial infarction following operation.

Postmortem Studies Nine patients dying, but who survived the operation from four months to six years (Table IV), came to autopsy. In all instances severe coronary disease was found.

TABLE IV

Case	Age	Survival Period		Cause of Death
		Years	Months	
3	53	2	6	Coronary insufficiency
6	61	6	1	Myocardial failure
9	51	5	8	Acute myocardial infarction
13	58		6	Myocardial failure
15	54	6	0	Coronary insufficiency
18	53	5	1	Coronary insufficiency
20	70	2	3	Cerebral hemorrhage
24	47	1	3	Acute myocardial infarction
31	54		4	Coronary insufficiency

DISCUSSION—The prognosis in cases of coronary artery disease varies greatly but, on the average, it is grave and the life expectancy is relatively short. The surgical means of producing an augmented coronary circulation is the first attempt to relieve patients of symptoms and to increase length of life. As has been stated by Beck, there must be sufficient good myocardium to maintain life or the improved coronary artery circulation will be ineffectual. Therefore, the candidates for the operation should be carefully selected, both as to extent and degree of coronary artery sclerosis and as to associated pathologic conditions.

It may be suggested that most of the cases with severe coronary artery disease did not survive the operation, and that those surviving did not improve. From postmortem examination of the patients who survived but who died subsequently, severe and widespread coronary artery disease

was demonstrated (Table IV) Cases 6, 9, 15, 18, 20, were greatly improved and were able to return to their accustomed jobs

In the 37 cases here reported the results of the operative survivals—both the patients who have since died and those who are still living—have been favorable in a large percentage of the cases The favorable effect of the long bed rest following operation may have played a part in the immediate result The total duration of life from the onset of symptoms and from the operation is found in Table V The operative mortality in the first 17 cases was 47 per cent, in the second 17 cases it was 35.3 per cent Patients should be selected for operation earlier in the course of the disease The mortality should be low in this type of case

TABLE V

Patients	Number	Per Cent	Average Duration of Life from Onset of Symptoms	Average Duration of Life Following Operation
Still living	14	37.8	9.0 years	6.9 years
Lived 4 months to 6 years	9	24.4	8.9 years	3.9 years
Dying postoperatively	14	37.8	4.1 years	

SUMMARY

1 Thirty-seven patients with coronary artery sclerosis and angina pectoris were operated upon by the Beck technic of providing additional blood supply

2 There were 14 postoperative deaths (37.8 per cent)

3 Nine patients who survived the operation, but died from four months to six years later, were studied after death The results in these patients were: Excellent—5, little or no improvement—4

4 Of the 23 patients who survived the operation, 14 are still living Of these nine are definitely improved and five show an increase in exercise tolerance and diminution in symptoms

5 Of the 23 patients who survived the operation, the results were as follows: Excellent—14, or 60.9 per cent, good—5, or 21.7 per cent, little or no improvement—4, or 17.4 per cent

6 The operation has given great relief to the 14 survivals Five of the patients who subsequently died were greatly benefited

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TOTAL GASTRECTOMY BY THE TRANSTHORACIC APPROACH

REPORT OF SEVEN CASES

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THE TECHNICAL ADVANTAGES of the transthoracic approach in cases of carcinoma of the stomach or lower esophagus invading the cardia are now well established. There remains, however, the necessity for greater experience with the operation before some of the particular details of the technic can be brought more nearly to a state of perfection. The operation of partial gastrectomy, removing the fundus of the stomach, the cardia, and a portion of the lower esophagus, is now being carried out with satisfactory results in several clinics. Experiences with the total excision of the stomach through the transthoracic route on the other hand have been few in number and most disappointing in their results. The operative mortality has been prohibitive. The difficulty in the few reported cases seems to have been with leakage from the suture line of the esophagojejunal anastomosis¹. This has doubtless been the result of the almost unavoidably great tension on the suture line caused by pulling the jejunum up to such a high level.

The physical variation in patients accounts for the fact that in a few the proximal jejunal loop can be brought up to a level an inch or more above the diaphragm without excessive tension, whereas in the majority the mesentery of this loop is too short. In two of the seven cases reported in this article it was possible to pull the upper jejunal loop high enough to perform an anastomosis slightly above the level of the diaphragm without an intolerable degree of tension. In the other five cases, although the loop could be brought to the level of the diaphragm in three of them, the level of invasion of the lower thoracic esophagus was so high that in order to cut well above the upper limit of the tumor it was necessary to transect at a level which was two to three inches above the highest point to which the jejunum could be drawn even under tension. It was the necessity for overcoming this difficulty which led to the development of the technic which is to be suggested here.

In 1942, the first report of a successful total gastrectomy using the transthoracic approach was made by Willy Meyer². In this case there was great tension on the suture line and, as a result, a jejunal fistula developed which discharged through the chest drainage tube. This fistula eventually closed spontaneously, and the patient recovered. Although the level at which the esophagus was cut across is not stated exactly, one might assume from the description that the anastomosis was not unusually high above the diaphragm. This was true of the first successful case in the Massachusetts General Hospital series. In three of the others, however,

TRANSTHORACIC GASTRECTOMY

the end of the esophagus and the apex of the jejunal loop could not be brought within two or three inches of each other

The fundamental principles of freedom from excessive tension on the suture line, and adequate preservation of blood supply to the parts, must be observed in this as in all other portions of the field of gastro-intestinal surgery. In any anastomosis involving the esophagus a careful layer-by-layer approximation of the cut edges must likewise be observed. As was pointed out formerly,³ the lack of a serosal layer in the esophagus alters

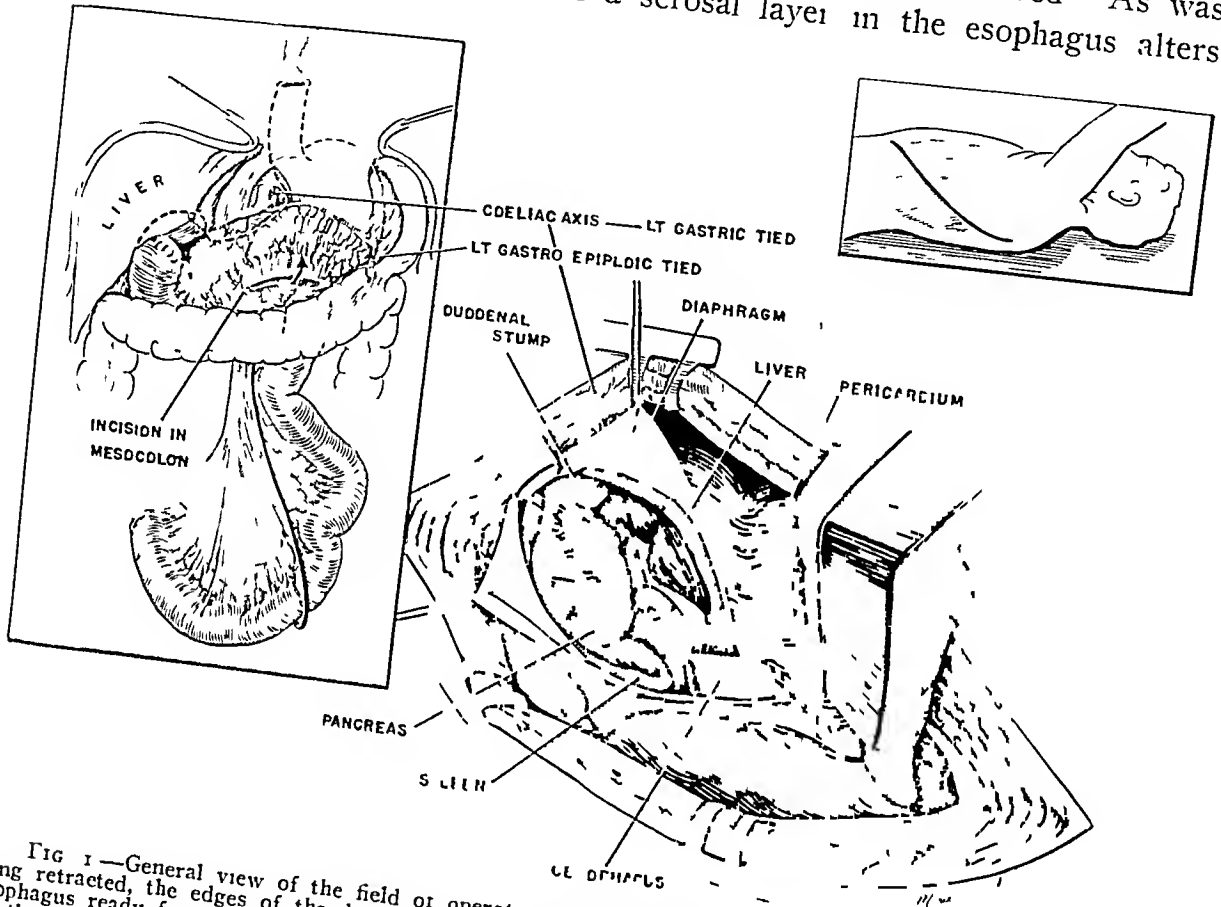


FIG 1—General view of the field of operation after the stomach has been removed showing the lung retracted, the edges of the diaphragm parted, the duodenal stump sutured, and the cut end of esophagus ready for the anastomosis. Insert upper right shows the direction of the incision over the ninth rib on the left side. Insert to the left shows the level of transection of the esophagus above the diaphragm, the line of incision in the transverse mesocolon, and the proximal loop of jejunum which is to be used for the anastomosis. Note the vascular pattern in the mesentery of this loop

the pattern of healing in such suture lines and great stress must be laid on an accurate suture of the mucosa which in the esophagus holds sutures better than the muscularis. This is to be accomplished best by means of a layer of fine silk placed in such a manner that the knots are tied on the side of the lumen. In the approximation of the muscular layer mattress sutures of fine silk give satisfaction with less tendency to tear out than common single sutures

OPERATIVE TECHNIC TO AVOID TENSION IN ESOPHAGOJEJUNOSTOMY

On being confronted with the problem of performing an esophago-jejunal anastomosis in a case where the two organs cannot be brought together by ordinary means, one's first impulse is to use the Roux procedure. The chief objections to this are, first, the danger of damage to

the vessels of the divided jejunal mesentery, and, secondly, the fact that an end-to-end anastomosis using the esophagus presents technical difficulties which are likely to compromise the result. The difficulty may be overcome as follows:

The usual transthoracic approach through the bed of the ninth rib is made. After removal of the entire stomach and closure of the duodenal stump, an opening should be made in the transverse mesocolon at a

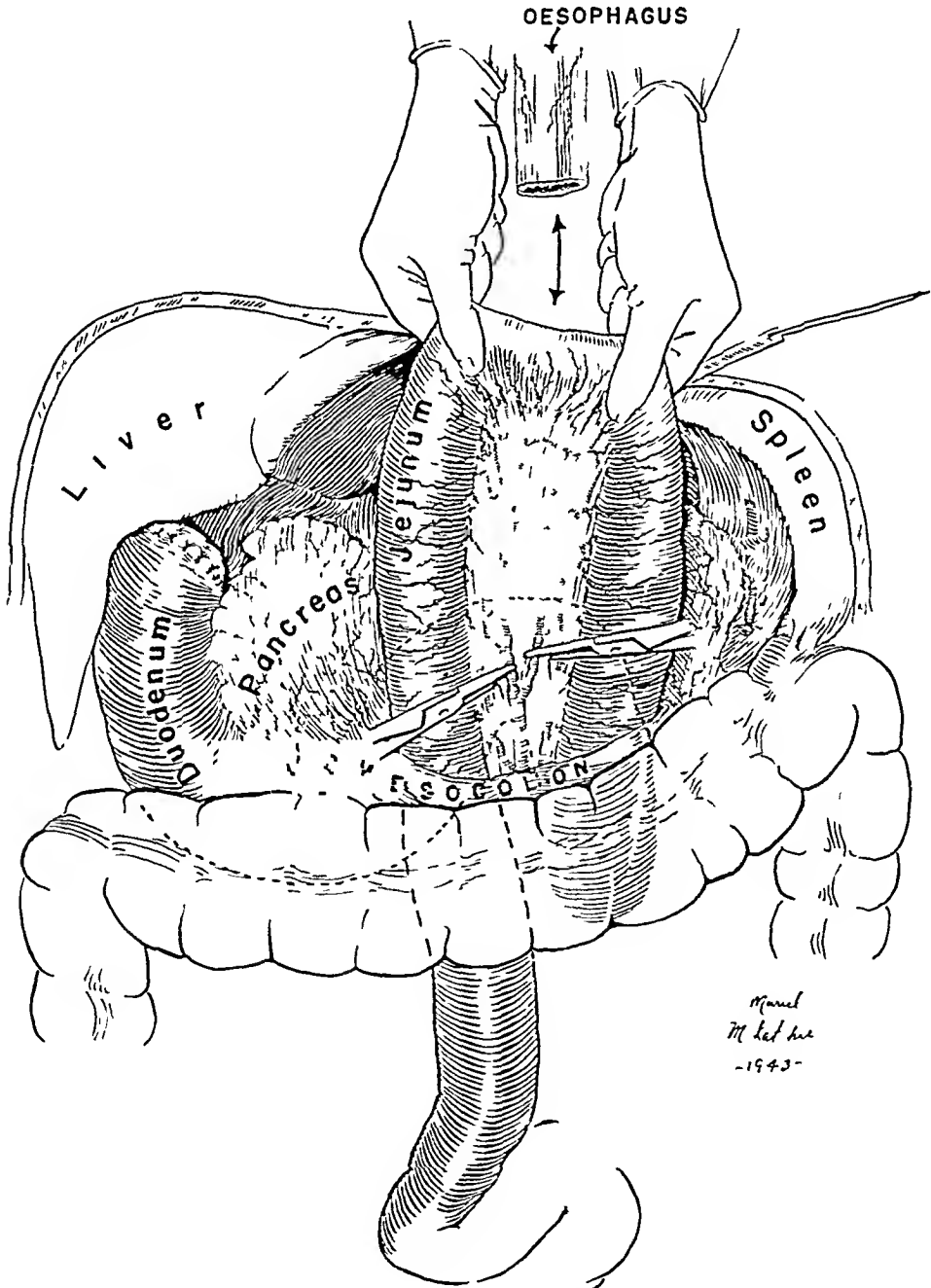


FIG 2—Proximal loop of jejunum drawn up through the transverse mesocolon. The pull of the mesenteric vessels makes it impossible to extend the apex of the loop much above the level of the diaphragm. Anastomosis with the esophagus not possible without release of the pull of the mesenteric vessels. Point of division of these vessels shown by hemostatic forceps in the drawing.

TRANSTHORACIC GASTRECTOMY

convenient point, taking care to avoid the middle colic vessels (Fig 1) The highest jejunal loop is then drawn up through the mesocolon, and in the majority of cases can be pulled no further than one or two centimeters above the level of the diaphragm (Fig 2) In every case the reason for

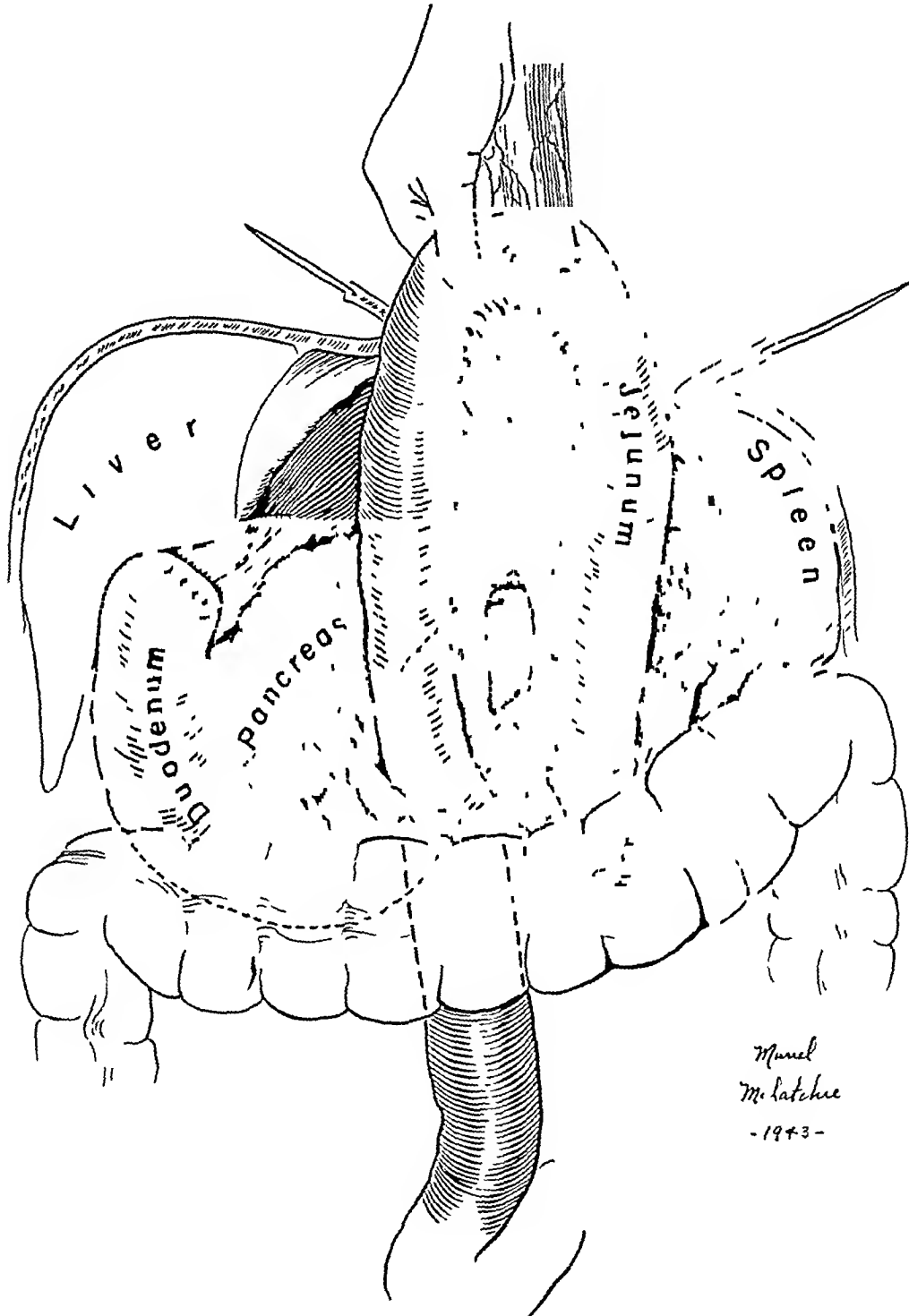


FIG 3—Marked release of tension after division of the mesenteric vessels makes it possible to bring the proximal loop of jejunum high above the diaphragm into the chest, and the esophagojejunostomy is performed without tension on its suture line

this is that the vessels of the mesentery are too short to allow the loop to go beyond that point although the bowel itself, if freed from the pull of the mesenteric structures, can be drawn up to any level In some cases a slight amount of relaxation of the pull results from dividing the ligament

of Treitz. This is rarely sufficient to make an appreciable difference. If, however, the main artery which supplies the proximal jejunal loop is sought out and cut between ties close to its origin from the superior mesenteric artery, and if the vein is treated likewise, the pull of the mesentery on the loop is greatly relaxed and its apex can be advanced as much as three inches into the chest above the level of the diaphragm (Figs 2 and 3). Great care must be exerted to avoid damage to the

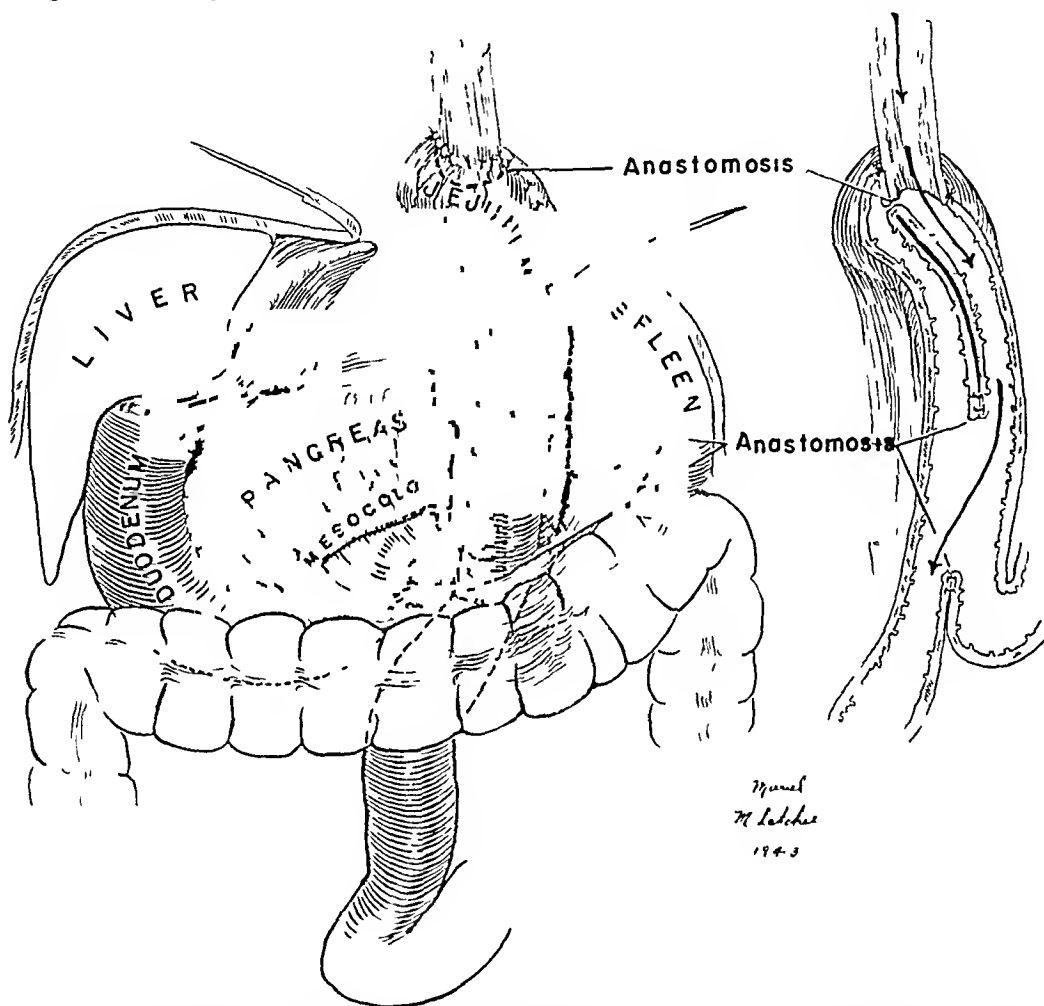


FIG 4—Completed anastomosis. Roscoe Graham technic used to reinforce the line of suture. Enteroenterostomy between the afferent and efferent limbs of the jejunal loop shown just above the level of the opening in the transverse mesocolon. Inset shows vertical section of lower esophagus and jejunal loop to which it has been anastomosed—enteroenterostomy shown.

collateral vascular arches during the division of the primary vessels and to avoid tearing or overstretching them as the loop is pulled up after division.

When the pull of the mesentery on the proximal jejunal loop has been relaxed by this means, the anastomosis can then be carried out without danger of its pulling apart later because of too much tension.

The exact technical details of the anastomosis may be varied to suit the indications of the individual case and the personal preference of the surgeon. I have used the Roscoe Graham method with great satisfaction.⁴ By this means a desirable extra reinforcement of the suture line is

easily obtained (Fig 4) It makes no difference whether the proximal (afferent) arm of the loop is used to wrap around the line of anastomosis or the distal (efferent) arm, providing an entero-enterostomy is carried out between the two arms of the loop, as Graham recommends It is important that the loop of jejunum be brought up in such a way that the afferent arm shall be short enough so as not to sag down below the level of the entero-enterostomy In this way puddling of food in the proximal arm and in the duodenum can be avoided It is not necessary to suture the divided jejunal mesentery or the opening in the transverse mesocolon

After the anastomoses are completed the jejunal loop must be anchored by means of sutures to the mediastinal pleura and to the cut edges of the diaphragm as they are brought around it The remainder of the diaphragm is then closed with interrupted silk sutures and motion is minimized by crushing the left phrenic nerve within the thorax by means of a hemostatic forcep

The above method of relaxation of the jejunal mesentery followed by an anastomosis using the Roscoe Graham method was employed with complete satisfaction in three of the seven cases reported Without it, in these cases, no anastomosis could have been carried out excepting possibly a modification of the Roux procedure

The operation of total gastrectomy followed by an esophagojejunal anastomosis has been performed seven times at the Massachusetts General Hospital In all, the choice of the transthoracic approach resulted from the fact that the tumor was close to, or had actually invaded, the cardia and in some of the cases the lower esophagus as well The decision to remove the entire stomach was made on the basis of the widespread involvement of the organ Two patients died postoperatively, both of sepsis In the first of these the death may be said to have resulted from a technical error because the suture line was found at autopsy examination to have separated in part If the procedure of dividing the vessels at the base of the proximal jejunal loop so as to relax the tension on the suture line had been followed in this case, there is reason to believe that the fatal result could have been avoided The widespread infection which was the cause of the death of the second patient could hardly have been avoided in the present state of our knowledge This patient was in a seriously debilitated condition resulting from obstruction at the cardia by a recurrent carcinoma of the stomach following a partial gastrectomy with a posterior Polya anastomosis In this case there was more opportunity for soiling to occur than in the average because of the necessity of undoing the previous anastomosis At autopsy there was peritonitis and empyema, but the esophagojejunal anastomotic suture line was intact

Each of the remaining five patients recovered promptly without major complications In the first two of these there was no difficulty in pulling

the proximal jejunum up to the level of division of the esophagus, which was not high. In the last three cases it was necessary to divide the esophagus at a relatively high level. In each of these cases it was impossible to bring the esophagus and jejunum together before the jejunal mesenteric vessels had been divided. In the last case the proximal loop could not be used at all because of extensive adhesions resulting from a former widespread acute peritonitis. In this instance it was necessary to use the next lower jejunal loop, and by dividing the vessels at the base of its mesentery it was possible to pull it well up above the level of the diaphragm into the thorax.

REPORT OF SEVEN CASES

Case 1—M G H No 294086 M O, female, age 55, entered the Massachusetts General Hospital March 21, 1941. She had had vomiting and weakness for the past year, and gradually increasing difficulty in swallowing. In the attempt to relieve her various forms of treatment had been carried out, including cholecystectomy three months prior to admission.

Examination showed a pale, ill-nourished woman. Her blood chemistry was essentially normal, and her Hinton negative. Roentgenologic examination showed a carcinoma of the lower third of the esophagus extending to the mid-portion of the body of the stomach. There were no visible metastases in the chest. Esophagoscopy showed no positive evidence of neoplasm and biopsy was unsatisfactory. Three centimeters above the cardia the mucosa looked red, and there were white plaques.

Operation—April 2, 1941. A transthoracic total gastrectomy with esophagojejunostomy, splenectomy, and partial pancreatectomy was performed. Under intratracheal gas-oxygen-ether anesthesia, the patient was placed on her side and an incision made along the entire length of the tenth rib on the left, which was exposed and resected subperiosteally. This rib was chosen because it was partly floating and probably, therefore, not the lower fixed point of the thoracic cage. The left lung was found free, was retracted upward, and the esophageal hiatus exposed. The phrenic nerve was paralyzed by crushing it as it crossed the pericardium, and the diaphragm was then opened in the direction of its fibers from the esophageal hiatus laterally. This exposed the spleen and stomach. Exploration revealed no evidence of liver metastases. The pelvis was free. Within the fundus of the stomach there was a large, hard tumor mass which extended into the lower inch of the esophagus. There were numerous firm nodes along the left gastric vessels. The esophagus was freed up above the tumor and a tape passed around it. The vasa brevia were clamped, cut, and ligated and the lesser omental bursa thus exposed and explored. The growth seemed resectable and dissection was, therefore, begun along the lateral aspect of the stomach. The peritoneum was reflected medially and numerous nodes were found near the splenic pedicle. The omentum was now opened along the greater curvature and a generous segment of it excised. Dissection was carried towards the pylorus which was finally freed on both sides and then cut across between Kocher clamps just on the duodenal side. The stomach was reflected medially, separating the attachments of the gastrohepatic ligament, until it was entirely mobilized down to the left gastric pedicle. It then seemed wiser to undertake a block resection of the tip of the pancreas, spleen, and left gastric pedicle, and this was carried out without difficulty, thus freeing the entire stomach to the esophagus. The esophagus was transected above the growth. The duodenal stump was inverted with a running atraumatic suture reinforced with interrupted silk, and the jejunum identified at the ligament of Treitz and a loop brought up through a rent in the transverse mesocolon. This was barely long enough to

reach the cut end of the esophagus. A little more length was secured by partially cutting the ligament of Treitz. A careful esophagojejunal anastomosis was performed, using many interrupted silk sutures in two layers, one mucosal and one muscular, with numerous sutures posteriorly to suspend the jejunum to the crura of the diaphragm. There was edema of the medial side of the esophagus through which the stitches tore, and this portion of the anastomosis was not completely satisfactory for this reason. An entero-enterostomy was performed between the two layers of jejunum and brought to lie just below the opening in the transverse mesocolon, which was loosely closed around them. A leaf of omentum was brought up to cover the jejunum and the region of the anastomosis, and the diaphragm reapproximated in two layers around it. A catheter, for drainage of the chest, was brought in through the next lower interspace posteriorly, and the chest wound closed in layers.

Pathologic examination showed the specimen to contain carcinoma of the stomach, with extension to the pancreas and esophagus, and metastases to the regional lymph nodes.

The patient had a severe febrile reaction following the operation. Her chest was aspirated on several occasions, and bloody, foul-smelling fluid obtained. There was drainage from her chest tube, at first thick and small in amount, then thin and copious, resembling the large return from her nasal tube. Roentgenograms showed a combination of fluid and atelectasis on the left side. She was treated by means of sodium sulfapyridine and transfusions, but continued to go downhill and died, nine days after operation. At autopsy, she was found to have empyema and pericarditis resulting from almost complete separation of the anastomotic suture line.

Case 2—M G H No 132669 G W, male, age 46, entered the Massachusetts General Hospital September 17, 1941. Three years before entry he had had a subtotal gastrectomy for what had been thought to be gastric ulcer, but pathologic examination of the specimen proved it to be carcinoma. For the past five months he had had increasing dysphagia with marked loss of weight. Gastro-intestinal series five days before admission showed no evidence of obstruction or metastasis in the esophagus, stomach, or in the anastomosis. Twenty-four hours prior to admission he had developed generalized periumbilical and lower abdominal pain, with nausea but no vomiting. The pain localized in the right lower quadrant and he was sent to the hospital.

Examination showed the patient to be a thin but well-developed man, with several small hard nodes in the left supraclavicular fossa. The chest and heart were negative. There was the sensation of a mass, in the right upper quadrant, and a question of spasm. There was slight spasm but no mass in the right lower quadrant, with localized tenderness about McBurney's point. Rectal examination showed fairly acute tenderness and fullness on the right.

A diagnosis of acute appendicitis was made, and the patient was operated upon. A perforated appendix was found. His convalescence was uneventful except for extensive infection of the wound.

Laboratory studies of his blood showed 345 red cells, 12,600 white cells, and a hemoglobin of 70 per cent on admission.

Thirteen days after appendicectomy roentgenologic examination of the esophagus showed what was interpreted as either cardiospasm or extrinsic pressure just above the hiatus. Subsequent roentgenograms revealed a mass involving the lower end of the esophagus, as well as the medial aspect of the fundus of the stomach, with the greater portion of the mass apparently outside the mucosa. These findings were interpreted as being due to recurrent carcinoma.

Esophagoscopy was performed October 6, 1941. There was a small amount of brownish, granular material in the lumen which was readily sponged away. The mucosa throughout the esophagus showed slightly enlarged rugae and seemed a little

redder than normal, but hardly enough to make a diagnosis of esophagitis. Bougies sizes No 12 to 22 passed readily through the cardia into the stomach. Examination was essentially negative, and it was felt that if the symptoms persisted, it might be wise to use the mercury bougie.

First Operation—It was decided that exploratory celiotomy was indicated, and this was undertaken October 18, 1941. A vertical left rectus incision was made, and through this the abdomen was explored. There was found to be apparently a mass of malignant disease in the lymph nodes around the left gastric vessels. It seemed to be loosely attached to the posterior tissues. The portion of the stomach which was left after the gastric resection was wrapped over the tumor, which had pushed from the medial side into the region of the cardia, where it produced a crescentic slit-like opening into which it was impossible to push the finger through the anterior stomach wall. The region of the gastrojejunostomy appeared to be perfectly smooth and there was no evidence of disease anywhere except as described. The liver seemed to be free from metastases. A jejunostomy was performed, taking care to leave a long proximal loop in case an excision should be undertaken through the lower part of the chest. The patient's course following exploration and jejunostomy was uneventful. He was comfortable and gained strength rapidly.

Second Operation—November 4, 1941. A transthoracic total gastrectomy and splenectomy were performed. A long oblique incision was made over the 9th rib on the left side. The entire length of the 9th rib was resected. The chest was opened. There were no adhesions, no fluid, and no evidence of pulmonary metastases. The diaphragm was then incised and the tumor was explored. It was essentially the same as previously noted, but it was soon discovered that the adhesions posteriorly were very dense. After considerable dissection it was finally decided that it could be removed. The operation was then proceeded with and, in order to get good access to the posterior attachment, the esophagus was divided early in the procedure. The stomach was then turned down and much of the posterior attachment in the region of the left gastric vessels was freed. The left gastric vessels were freed and the transverse mesocolon removed from its attachment to the stomach. The anastomosis was opened by cutting along the suture line and the cut end of the stomach inverted to prevent gross soiling during the manipulation of delivering the mass. The opening in the jejunum was sutured transversely with two layers of chromic catgut reinforced with several silk sutures. The tumor mass along with the entire remains of the stomach was then removed by cutting posteriorly, and in doing this a section of the pancreas had to be removed along with a portion of the splenic artery. The vessels were tied and the spleen was then quickly removed because of its lack of blood supply. At this point, considerable bleeding was noticed and the stump of the splenic artery was immediately exposed and found to be bleeding because the tie had come off. It was quickly secured and carefully tied with a heavy silk ligature. An end-to-side anastomosis was then performed between the apex of the jejunal loop above the jejunostomy and the cut end of the esophagus. The incision in the jejunum was placed transversely across the length of the bowel and the loop was wrapped around the lower end of the esophagus, after the Roscoe Graham method. An entero-enterostomy was established between the two arms of the jejunal loop. Some omentum was brought up and the loop was held up by attaching the leaves of the pulmonary ligament to it. The diaphragm was then closed, but care was taken to avoid constriction. It was sutured in several places to the two arms of the jejunal loop. The phrenic nerve was crushed, and the chest closed without drainage. Eight Gm of sulfanilamide were distributed in the upper abdomen and lower part of the left hemithorax.

Pathologic examination of the specimen removed was reported as adenocarcinoma of the stomach, recurrent in the wall of the lower esophagus.

Postoperative Course—Following resection, the patient made an excellent immediate recovery, but on the third day an aspiration of the left side of his chest yielded 700 cc of serosanguineous fluid. A culture of this showed abundant growth of *B. coli* and nonhemolytic streptococci. On the fifth postoperative day it was apparent that he had fluid at his right base and there was also evidence of pneumonia in the right lung. He did not develop much elevation of temperature, but it was apparent that he was losing ground. Two days after this he suddenly became dyspneic. Seven hundred cubic centimeters of purulent fluid were removed from the left side of his chest. He was placed immediately in an oxygen tent, but died suddenly the same afternoon. Autopsy revealed that there was pus in the upper part of his abdomen, in the left side of his chest, and also an empyema on the right side with evidence of bronchopneumonia in both lungs. The suture line was intact and there was no evidence of any leakage.

The presumption is that this patient, already depleted by long-standing starvation and the presence of a large carcinoma, did not have sufficient resistance to withstand the infection which resulted from the soiling of the field at the time of operation.

Case 3—M. G. H. No. 361509. M. K., male, age 56, was admitted to the Massachusetts General Hospital, June 27, 1942, complaining of anorexia and abdominal pain. Three years before admission he had had a strangulated right inguinal hernia repaired. The hernia recurred one month later, and at that time he began to have symptoms of low-grade intestinal obstruction with cramps, "gas pains," rare vomiting, and occasional diarrhea. Two years before admission, he had been operated upon after roentgenologic examination of the gastro-intestinal tract showed a mass in the large intestine. The abdomen was explored, and a large, apparently inoperable carcinoma of the stomach, located on the lesser curvature and extending almost to the esophagus, had been found. This involved the entire lesser curvature, according to the surgeon, and had metastasized to the aortic nodes, the sigmoid, and the bladder region. The prognosis was considered hopeless and no further operative procedure was attempted.

He remained in the hospital for seven months following the exploratory celiotomy, and at discharge weighed 120 pounds. Since that time he had remained in much the same condition, with poor appetite, constipation, gas and borborygmus. His diet consisted of milk and eggs. He complained of knife-like periumbilical pain coming on usually 15 minutes after eating and persisting for hours or days. On the other hand, he had gone as long as a week without distress. He had gained about 30 pounds in the past year and a half, but was too weak to do anything but very light work. He had had no vomiting, no nausea, and had never noticed blood in the stools. He was almost always conscious, however, of gas and intestinal rumbling. He remained obstinately constipated and required large doses of mineral oil. He had noticed recently that his ankles were swelling after he had been up for some hours. He had no urinary symptoms other than nocturia.

Because of the persistence of his symptoms the patient reported to the Massachusetts General Hospital Out-patient Clinic. A gastro-intestinal series was advised, and when fluoroscopy revealed dilated loops of small bowel he was admitted to the hospital at once and a Miller-Abbott tube passed.

Physical examination revealed a well-developed, poorly nourished, apathetic, middle-aged male. The heart was normal. Blood pressure 105/60. The chest was negative. The abdomen was flat. Peristalsis was active. The liver and spleen were not felt. Rectal examination was negative.

Roentgenologic examination before admission showed markedly dilated loops of small intestine. Fluoroscopic examination of the abdomen four hours after the motor

meal had been given showed the dilated loops to be probably mid- and lower-jejunum. The obstruction could not be outlined because of insufficient filling of the loop, which was dilated and contained a considerable amount of fluid in addition to the small amount of barium. It was thought that the obstruction was near the pelvic brim, and the patient was slightly tender in this area on palpation. A barium enema showed inadequate filling of the midsigmoid but gave no other definite information.

Laboratory studies showed the patient to have a hypochromic anemia, with a red blood cell count of 3,32, white count of 11,600, and photohemoglobin of 6.1 Gm. The differential showed 55 polymorphonuclear cells, 8 large lymphocytes, 28 small lymphocytes, 7 monocytes, 1 basophil, and 1 young polymorphonuclear cell. The serum protein was 3.5 per cent, the chloride 105.9 mg per cent, nonprotein nitrogen 23 mg per cent, and the CO_2 combining power 24.1 mg per cent. Urinalysis showed albumin ++++, with 20 to 30 hyaline or granular casts per high power field, and 5 to 10 white blood cells.

First Operation—July 2, 1942. A resection of the terminal ileum, with enterointerostomy and resection of the sigmoid, with colostomy, were performed. The abdomen was opened through a right paramedian incision. The upper three-fourths of the small intestinal tract was normal in appearance. The lower fourth was a matted mass of bowel, greatly dilated and fibrosed. It was adherent in the left lower quadrant to the sigmoid and bladder. Distal to this point, which was about six inches proximal to the ileocecal valve, the ileum was collapsed. The large bowel was normal otherwise. Palpation of the stomach revealed a very large carcinoma of the fundus which was freely movable and did not appear to involve the esophagus. There were a few small, hard, nodules in the liver, one of which was removed for biopsy. The bowel was dissected free from the sigmoid and a fistulous opening was found to exist between the two. There was some tissue in the sigmoid which suggested malignant disease.

The large matted mass of intestines was resected. Six inches of the terminal ileum were saved. The end of this and the distal end of the upper ileum were turned in with running catgut for mucosal sutures and interrupted Halsted mattress sutures of cotton. A side-to-side anastomosis was performed between the two portions of ileum, using two layers of running catgut sutures. The proximal end of the anastomosis lay inferior to the distal end. The Miller-Abbott tube had descended to this level and the tip of it was passed through anastomosis.

Because of the opening in the sigmoid and the question of malignant disease in it, this was resected and the cut ends brought out through a McBurney incision in the left side of the abdomen. The loops were not sutured together as it was intended to reanastomose them by an end-to-end suture after resection of the stomach. The abdomen was closed in layers after sprinkling the peritoneum with sulfanilamide powder.

Pathologic examination of the specimens removed showed a $1 \times 0.5 \times 0.2$ cm fragment of liver which was almost completely replaced by white, glistening friable tissue. This proved to be metastatic adenocarcinoma. There were approximately two feet of ileum which was thrown into six knuckles, firmly bound to each other by dense bands of old fibrous tissue. In one place these adhesions formed a slightly elevated gray plaque, measuring 1×2 cm. At this point the wall had an average thickness of four millimeters. Elsewhere the average thickness was two millimeters. The mucosa was negative. Also submitted was a portion of large bowel, measuring eight centimeters, which was grossly negative. A diagnosis of intestinal obstruction due to adhesive bands was made.

Postoperative Course—The patient did well following operation until the 17th day, when both legs were found to be swollen about the ankles. Ten days later he had a slight fever lasting for two days, and complained of some pain in his right

chest Roentgenologic examination of the chest showed scarring in the right lung and old pleurisy, consistent with healing infarcts. Because of this and especially because of his prospective long stay in bed, it was felt that this patient should have ligation of both superficial femoral veins. This procedure was carried out on August 2, 1942.

Barium examination of the esophagus and stomach, on August 5, 1942, failed to reveal any pathology. There was considerable food in the stomach. The duodenum was large throughout its length. The first two loops of jejunum were not dilated. No further examination was made.

Second Operation—August 11, 1942. Trausthoracic total gastrectomy and splenectomy were performed, with esophagojejunostomy and entero-enterostomy. Under intratracheal ether anesthesia, the ninth left rib was resected. The lung collapsed satisfactorily on opening the pleura. The diaphragm was then opened and it was ascertained that the lesion was resectable. The left phrenic nerve was then crushed. A gastrectomy was performed removing one and one-half inches of esophagus, the lower end of which was involved in the carcinoma. The diaphragm was then severed in its entirety, leaving about one centimeter around the esophageal hiatus. This was done in order to use this portion of the diaphragm as a support for the jejunum, as it was found impossible to bring the jejunum within the thorax without undue tension. An end-to-side anastomosis was performed after freeing up the esophagus and bringing it down through the esophageal hiatus. Three rows of interrupted cotton mattress sutures were used. The outer layer was between the diaphragm and jejunum, the inner two layers were between the esophagus and jejunum. There were very few if any metastatic nodes to be noted. A few small metastatic nodules were palpable in the liver. As the spleen was in the way of the stomach it also was resected along with a portion of the pancreas. An entero-enterostomy was performed between the distal and proximal jejunal loops, as there seemed to be a little kinking of the distal jejunal loop where it was sutured to the diaphragm. The diaphragm was then closed with interrupted cotton and a running catgut suture. The chest wall was closed in layers. A whistle-tip catheter was brought out through the ninth interspace. Sulfanilamide was used around the anastomosis and in the thoracic wound.

Pathologic Examination—*Gross*. The specimen showed a totally resected stomach including 1 cm of esophagus and 2 cm of duodenum. It measured 18 cm in length and 14 cm in circumference. It contained in its center a large, indurated, fungating, partially annular neoplasm measuring 10 cm in length, 16 cm in circumference and 5 cm in thickness. The serosa was smooth but moderately elevated over the nodular, firm, external surface of the lesion. The mucosa was smooth, pale, and pebbly except for the neoplastic area where there were hard fungating nodules measuring up to 3 cm in maximum diameter protruding up to 2 cm above the surface. There were some superficial necrotic areas. No lymph nodes were attached to the specimen, but a separately submitted lymph node was firm, gray, and measured 8 mm in diameter.

Pathologic Diagnosis. Adenocarcinoma of the stomach.

The patient's recovery from operation was uneventful, and his subsequent progress excellent. On September 5th the colostomy was closed and he was discharged 18 days later, six weeks after the gastrectomy. On December 6th, four months after the gastrectomy, he was in only fair condition and probably beginning to fail because of the metastatic disease in the liver.

Case 4—M G H No 68281 B S, female, age 59, was admitted to the Massachusetts General Hospital on December 14, 1942. She had had two previous admissions, one in 1937 for removal of a left temporal meningioma and the second in 1941 for ligation of the left saphenous vein. Her complaint at this time was of increasingly severe anorexia for the past six or seven months accompanied by weight loss of approxi-

mately 30 pounds. Because of this she had gradually eaten less and less and, for the past few weeks, had taken nothing except milk. During the past two months she had had epigastric pain which radiated around the right side to the back. Associated with this pain, which was unrelated to meals or to the type of food eaten, was a feeling of fullness in the abdomen, particularly in the epigastrium. She had been nauseated but had vomited only one or twice. There had been no hematemesis. There had been no change in bowel habit and no tarry or bloody stools. She had had no cough, chest pain, or hemoptysis. She had had a gradually increasing feeling of weakness associated with some dyspnea on exertion. There was a history of cancer in a number of members of her family.

Physical examination showed a middle-aged, pale woman, with evidence of recent weight loss. There were a few small nodes in the left axilla. There were no supraclavicular nodes. The heart was enlarged by percussion 15 cm. outside the midclavicular line. There was slight splitting of the first sound at the apex with faint soft systolic murmur and an occasional extra systole. Blood pressure 140/60. The lungs were clear. Abdominal examination showed a relaxed and flabby abdominal wall with numerous striae. The liver was palpable on deep inspiration about two fingers breadth below the costal margin. It was smooth and not tender. There was no palpable mass.

Laboratory studies showed a white blood cell count of 6700, a red count of 580, and hemoglobin of 100 per cent. Stool was guaiac-negative. Gastric analysis before histamine revealed guaiac ++++ reaction, free acid 0, combined acid 16, after histamine, analysis of 15 oz. of mucoid, grossly bloody fluid showed no free acid, combined acid 34, total acid 34. Serum protein 60 mg. per cent.

Roentgenologic examination of the esophagus was not remarkable. The lumen of the stomach, however, was markedly decreased in size. The stomach wall was thickened and the mucosa was destroyed from the fundus to a point about six centimeters proximal to the pylorus. The duodenum and upper jejunum were not remarkable. The appearance was that of scirrhus carcinoma. There was no definite evidence of involvement of the lower esophagus. Examination of the dorsal and lumbar spine was negative. The lungs were clear and the heart not remarkable.

Operation—December 23, 1942. A transthoracic total gastrectomy, with esophagojejunostomy, splenectomy, and entero-enterostomy, was performed. A long incision was made over the course of the 9th rib on the left side, and the 9th rib was resected. The lower lobe of the lung was quite adherent and had to be freed so as to get at the diaphragm. The diaphragm was divided after first paralyzing the phrenic nerve with novocain. The stomach was explored and it was found that it could be brought up easily. There were no adhesions and there was no invasion of any adjacent structure excepting the hilum of the spleen where the growth had apparently begun to extend. This made it necessary to remove the spleen along with the stomach. The major portion of the stomach was involved so that a total gastrectomy was the only logical procedure.

The diaphragm was divided completely through the hiatus. The phrenic nerve was crushed and the stomach was freed by cutting the diaphragmatic attachments and the left gastric vessels. The spleen was then removed, tying the artery and vein separately, and the incision was carried between the spleen and the pancreas and along the gastrocolic ligament. At this point, it seemed to be easier to cut across the esophagus and turn the stomach up so as to get access to the duodenum. This was, therefore, done, using Dr. Smithwick's special clamp and closing the end temporarily with a basting-stitch of silk. The duodenum was then freed. An attempt was made to tie it, but the tie slipped off and it then became necessary to invert it in the usual way, using a Connell suture on the inner layer, a second layer of running

TRANSTHORACIC GASTRECTOMY

Lembert stitch, and an outer layer of Lembert mattress sutures, using interrupted silk. The upper loop of jejunum was then brought out. It had a very short mesentery so that it was impossible to bring the loop very high into the chest. A satisfactory anastomosis was made, however, using the end of the esophagus to the side of the jejunum with two layers of interrupted silk sutures, an inner layer in mucous membrane and an outer layer of mattress sutures in the muscularis.

An entero-enterostomy was performed between the two arms of the jejunal loop using two layers of sutures, catgut inside and fine silk on the serosal side. In doing this it seemed wise to fold the jejunum over and wrap it around the anastomosis and esophagus, in very much the same way as advocated by Roscoe Graham. This was done using silk sutures. The jejunal loop all around to the anastomosis was firmly fixed to the posterior cut edges of the diaphragm with interrupted silk sutures. A portion of omentum was brought up and fixed around the anterior part of the anastomosis. A stomach tube was then threaded down through the esophagojejunoanastomosis into the proximal arm of the loop and down through the entero-enterostomy into the distal arm. This route was chosen because it seemed to be the most direct.

About six Gm of sulfanilamide was introduced, some in the upper abdomen and some in the chest. The diaphragm was closed with interrupted silk sutures and, after putting a catheter in the interspace below, the chest was closed in layers in the usual way. The lung was thoroughly reexpanded before chest closure was made.

Pathologic Examination—The specimen showed a complete stomach to which was attached a 300-Gm normal-appearing spleen. The stomach measured 15 cm on the lesser curvature and 20 cm on the greater curvature. The wall was 7 mm thick in the area of the tumor, which occupied the proximal 10 cm of the specimen. The tumor stopped abruptly in the distal third and here the mucosa was intact, normal in appearance, with walls less than 5 mm thick. The serosa over the tumor-bearing area was red and brawny, elsewhere smooth and shiny. Dense tissue seemed to be growing into the fat at the lesser curvature. One soft lymph node was found. *Pathologic Diagnosis* Scirrhous carcinoma and arteriosclerosis of the spleen.

The patient's postoperative convalescence was comfortable and complicated only by thrombophlebitis occurring on the 22nd day after operation, because of which the left superficial femoral vein was ligated and jelly-like clot removed both distally and proximally.

Case 5—M G H No 387483 W S, male, age 49, entered the Massachusetts General Hospital, December 31, 1942, having been referred by his local doctor with a diagnosis of inoperable carcinoma of the stomach. About one and one-half years previously the patient had been studied elsewhere because of severe hematemesis, and had been told that he had ulcers of the stomach. He had been treated medically, with apparently satisfactory remission of his symptoms. About four months before admission, however, because of vague digestive disturbances and vomiting, a roentgenologic examination resulted in a diagnosis of carcinoma of the stomach being made. He had had no more hematemesis. An exploratory celiotomy had been performed, and an apparently inoperable growth found. The carcinoma was large, was located at the very upper end of the lesser curvature and appeared to extend into the lower esophagus, with posterior extension of the lesion. Following the operation the patient had felt poorly, had lost about 30 pounds in weight, had vomited almost everything he had eaten, and had had increasing difficulty in swallowing. He had had a little abdominal pain, but his main problem was that of starvation. He complained of increasing constipation, but had had no melena or bloody stools. He had always been well up to the time of his present illness.

Physical Examination—The patient was a pale, somewhat cachectic white male, showing evidence of chronic wasting disease. There were almond-sized bilateral, non-

tender inguinal nodes and shotty epitrochlear nodes. The chest was emphysematous, the diaphragms low, and the costal margins flared. The abdomen was scaphoid. There was a well-healed, recent, nontender, right upper midrectus scar. The liver margin was soft and not tender at the right costal margin. In the right epigastrium there was a deeply felt, nontender resistance, with a questionable mass.

Roentgenologic examination of the gastro-intestinal tract showed a defect in the lower end of the esophagus extending from the cardia and continuing around the



FIG 5—Case 5. Preoperative roentgenogram of stomach showing large filling defect involving lower esophagus and fundus and proximal two thirds of lesser curvature of stomach.

stomach in an annular fashion. The involvement extended down upon the stomach to the distal third, where free peristalsis began and the stomach wall was quite flexible. The duodenal bulb was normal. There was no great amount of obstruction at the cardia. The findings were those of carcinoma of the cardia involving the lower end of the esophagus and adjacent stomach (Fig 5). Examination of the chest showed no evidence of metastases.

Laboratory studies showed the white blood cells 4900, the red cells 418, hemo-

TRANSTHORACIC GASTRECTOMY

globin 100 per cent Examination of the stools gave a positive guaiac test The vomitus showed a negative guaiac reaction

Operation—January 12, 1943 A transthoracic total gastrectomy was performed A long oblique incision was made along the course of the ninth rib on the left side The entire ninth rib was resected There was no fluid in the chest cavity The lung felt normal The tumor could be felt through the diaphragm The diaphragm was opened and the tumor explored It was a very large carcinoma involving the lower esophagus as far as a point about two inches above the diaphragm and extending down the lesser curvature and posterior wall of the stomach almost to the pylorus The posterior wall was adherent to the pancreas and it was necessary to remove a small portion of the pancreas along with a loop of the splenic artery This made it necessary to perform a splenectomy

The entire stomach and lower esophagus were freed The duodenum was grasped



FIG 6—Case 5 Photograph of the specimen consisting of the entire stomach, including a portion of lower esophagus

with the Jones clamp and inverted, using the Jones clamp method This was accomplished without difficulty and reinforcing sutures were used to hold the pancreas over the inverted duodenal end The esophagus was then divided at a point about three or possibly more, inches above the level of the diaphragm The proximal loop of the jejunum was then brought up through an opening in the transverse mesocolon, and it was found that this loop could not be brought any closer than three or four inches from the cut end of the esophagus The apex of the loop was barely above the level of the hiatus of the diaphragm The large vessel at the base of this loop of jejunum was, therefore, divided between two ties, and it was found that this gave enough relaxation of the pull on the loop to allow it to be brought into the chest as far as necessary, and a very comfortable anastomosis, without tension, was made The jejunal loop was fixed to the edge of the diaphragm posteriorly and to the mediastinal pleura Anastomosis was made, end-to-side using three layers, on the

proximal arm of the jejunal loop. The distal arm was then wrapped around, by the Roscoe Graham method, so as to completely cover over the anastomotic suture line. An entero-enterostomy was then performed between the two arms of the jejunal loop. It was found after this was done that the entero-enterostomy lay at a point just above the level of the diaphragm.



FIG 7—Case 5. Postoperative roentgenogram showing the wide open esophagojejunal anastomosis several inches above the level of the diaphragm, which is indicated by the constricted appearance of the jejunal loop at that point.

The Levin tube was brought down through the esophagojejunostomy, but it could not be put through the jejunojejunostomy. Silk technic was used throughout excepting for the entero-enterostomy which was done with catgut.

The phrenic nerve was crushed and the diaphragm was sutured around the jejunal loop after covering the entire loop and both anastomoses with a piece of omentum.

which came up easily Suture of the diaphragm was then completed A catheter was led out through one of the lower interspaces and the wound closed in layers

Pathologic Examination—Gross The specimen consisted of an entire stomach including a portion of the esophagus, measuring 10 cm on the lesser and 25 cm on the greater curvature (Fig 6) On the lesser curvature there was a large, ulcerated fungating, yellowish-gray, granular, infiltrating mass $11 \times 6 \times 1$ cm almost completely encircling the cardiac end of the stomach except for an area 2 cm wide The mass infiltrated the muscularis of the lower portion of the esophagus and approximately 6 cm of the lesser curvature The mass infiltrated the muscle wall and involved the anterior and posterior surfaces of the serosa which was hemorrhagic reddish-brown Otherwise the mucosa was slightly edematous No regional lymph nodes were found Submitted separately was a normal-appearing spleen measuring $12 \times 8 \times 3.5$ cm, weighing 158.5 Gm, and a lymph node measuring $2 \times 1 \times 1$ cm was also present The pulp was deep purple and firm *Pathologic Diagnosis* Adenocarcinoma of the stomach, acute and chronic gastritis, and moderate arteriosclerosis of the splenic arterioles The lymph node showed diffuse fibrosis and a considerable amount of brown pigment This did not take the iron stain, and was probably carbon There were some foci of multinucleated giant cells which did not resemble those seen in tubercles

The patient made an uneventful recovery He was discharged within three weeks of the date of the operation At that time he was eating a six-meal bland diet with comfort Postoperative roentgenograms showed a well functioning anastomotic stoma (Fig 7)

Case 6—M G H No 295524, J C, male, age 54, was admitted to the Baker Memorial, at the Massachusetts General Hospital, December 30, 1942, complaining of substernal discomfort and anorexia One and one-half years previously he had begun to experience substernal discomfort and tenderness, together with loss of appetite These symptoms came on suddenly, the patient had always been well although he had never been a very heavy eater He described his symptoms as a "sick feeling" which came on irregularly, during which time he would feel nauseated but would not vomit, though he would occasionally have regurgitation of a little fluid These episodes were quite frequent, lasting from 15 to 20 minutes, and were only slightly relieved by soda They bore no constant relation to meals or exercise and continued up to the time of admission He had no dysphagia Shortly after the onset of these symptoms the patient had a gastric series, and three months before his present admission he had had a barium enema, both of which were negative He had been put on a bland diet after the first roentgenologic examination, but the anorexia had persisted, and during the next six months he had lost 20 pounds About four months before admission, however, there was a remission in his symptoms, his appetite improved somewhat, and he regained 10 pounds, but for the last three weeks he had had anorexia, again accompanied by a feeling of weakness and fatigue, and he had begun to lose weight again He thought he noticed dark stools on several occasions, but had had no bloody stools or hematemesis A week before admission he had had a second gastric series, and as a result of that was advised to be operated upon His father had died at 79 of cirrhosis and cancer of the liver, but there was no other family history of cancer

Physical Examination—The patient was a fairly well-developed and well-nourished man of middle age, pale, but apparently in no distress His heart was not enlarged Blood pressure 92/58 There was a soft irregular mass in the left epigastrium, fixed posteriorly, and not tender The liver edge was not palpable

Roentgenologic examination of the stomach showed the esophagus to be not remarkable Just distal to the fundus of the stomach the mucosal pattern appeared altered and in some places destroyed There appeared to be a small ulceration along

the lesser curvature of the stomach. The stomach appeared to be involved from a point 5 cm distal to the cardia down to the pylorus. There was no evidence of involvement or of extension through the pylorus. The findings were those of fairly extensive carcinoma of the stomach.

Laboratory studies showed white blood cells 5300, hemoglobin of 14.5 Gm. The stool showed a negative guaiac reaction. Hinton test was negative. Fasting blood protein was 4.7 per cent.

Operation—January 6, 1943. A transthoracic total gastrectomy was performed, with splenectomy and esophagojejunostomy and jejunal entero-enterostomy. A long oblique incision was made over the course of the ninth rib on the left. The entire ninth rib was resected and the chest was opened through its periosteal bed. The lung was not adherent. The tumor could be palpated through the diaphragm. It extended into the lower esophagus but not far in the thoracic portion. The diaphragm was opened and retracted with stay sutures. The liver was palpated and no nodules were found within it. The carcinoma extended along the lesser curvature from the pylorus to the cardia and, although the greater curvature was free excepting near the fundus, it was obvious because of the extent along the lesser curvature that nothing short of a total gastrectomy would be of any value.

There were a number of large lymph nodes near the cardia and also on both sides of the pylorus which seemed to be involved. These were all removed. It was necessary to remove the spleen in order to get proper access to the region behind the stomach. The lower esophagus was freed. The left gastric vessels were cut and tied. The anastomotic branches around the hiatus of the diaphragm and the vasa brevia were likewise cut and tied. The entire stomach was then freed, but in order to get good access to the duodenum it was necessary to cut across the esophagus first. This was done, using Doctor Smithwick's clamp. A basting-stitch was then used to close over the esophageal cut end, and the clamp was removed. The dissection was then carried down to the duodenum and in cutting around the lymph nodes which lay there so that they could be removed, the duodenum was partially torn. The remainder was cut across and the open duodenal end was sutured with a first layer of Connell sutures and a second layer of Lembert sutures of silk. This was reinforced by suturing it into the head of the pancreas and applying a piece of omentum over that. A rent was then made in the transverse mesocolon and the proximal jejunal loop was brought up through it. There was just enough slack in the jejunum to allow an anastomosis without tension. The Smithwick clamp was used again on the jejunum and an aseptic anastomosis was performed, placing the esophagus on the efferent arm of the jejunal loop. The afferent arm was then folded over the anastomosis by the Roscoe Graham method. Before the anastomosis was started the jejunal loop had been fixed posteriorly to the crura of the diaphragm and some of the mediastinal pleura. A three-layer suture was used. An entero-enterostomy was then performed between the proximal and distal arms of the jejunal loop, using two layers of catgut. An attempt was made to thread the nasal catheter through the anastomosis without success. It was, therefore, left in the lower esophagus. A long piece of omentum was brought up and sutured around the anastomoses, completely covering over the loop which had been brought up. The diaphragm was then sutured loosely around the jejunal loop. The entero-enterostomy was just below the level of the diaphragm. The opening in the transverse mesocolon was not sutured.

Two Gm of sulfanilamide was introduced in the abdomen and two in the chest. A catheter was brought out through the 9th interspace posteriorly, and the chest was closed.

Pathologic Examination—Gross. The specimen showed a totally resected, previously opened stomach including the pylorus, measuring 30 cm along the greater curvature and 12 cm along the lesser. A small (0.5 cm) piece of esophagus was also present.

TRANSTHORACIC GASTRECTOMY

Involving practically all of the lesser curvature and about a third of both anterior and posterior walls was a very hard, infiltrating tumor, measuring approximately 8 x 6 cm. The edges of the tumor were raised approximately 6 — 7 mm and the main bulk of the tumor was ulcerated, reddish-yellow, and granular. The tumor extended very close to the pyloric cut edge. The entire muscularis and serosa in the region of the tumor was definitely infiltrated, producing irregular grayish-white subserosal plaques.

Pathologic Diagnosis Adenocarcinoma, with metastases to regional lymph nodes.

Roentgenologic examination of the chest three days after operation showed diffuse haziness throughout the left side, probably due to a small amount of fluid. There was no evidence of appreciable mediastinal shift.

The patient's postoperative course was uneventful and uncomplicated except for parotitis, which developed a week after operation.

Case 7—M G H No 391651 I P, male, age 57, was admitted to the Baker Memorial, January 29, 1943 because of what was thought to be a gastric ulcer. He had been perfectly well until ten months previously when he first noticed the onset of a tired feeling. His physician said that his blood was low and gave him vitamins and iron. This improved him considerably. In May, 1942, he had had a three-week episode of diarrhea, without blood or other symptoms. This had cleared spontaneously and except for occasional abdominal discomfort and gas he had been well until about eight weeks prior to admission when he had had another attack of diarrhea without other symptoms. Four weeks before admission he had vomited about two cupsful of blood, had fainted, and had been taken to a local hospital. He soon recovered, and a gastrointestinal series showed what was thought to be a gastric ulcer. He was, therefore, referred to the Massachusetts General Hospital for gastroscopy and treatment. He had had no nausea, vomiting, or cramps except as previously mentioned. His appetite had been good. He had lost about 12 pounds during his recent hospital stay but had regained some of that. He had no other symptoms.

Physical Examination—The patient was a well-developed and well-nourished middle-aged white male. The heart and lungs were apparently normal. Abdominal examination was negative. Rectal examination was negative. There was no rectal shelf.

Laboratory studies showed a photohemoglobin of 10.7 Gm., serum protein 5.2 per cent, N P N 32 mg per cent and chloride 105.4 mg per cent. The Hinton test was negative.

On January 30, 1943, gastroscopy was attempted but at the cardiac orifice the instrument met with complete obstruction, and no view of the stomach could be obtained. It was felt that the findings were consistent with neoplasm involving the upper part of the stomach close to the cardiac orifice and that the case was a suitable one for transthoracic gastrectomy.

Two days following gastroscopic examination the patient suddenly vomited about 700 cc of bright red blood. His blood pressure fell to 90/50. He was transfused a number of times, with good response.

Operation—February 10, 1943. A transthoracic gastrectomy with esophagojejunostomy, entero-enterostomy, and splenectomy were performed. A long oblique incision was made along the left side of the chest and the ninth rib was resected. There were a number of adhesions between the lung and diaphragm. These had to be separated. The lower end of the esophagus was identified and freed-up. A tape was passed around it. The diaphragm was opened. The growth was found to be operable and the phrenic nerve was, therefore, pinched. The growth extended from about 15 cm below the cardiac orifice almost to the pylorus, and it was obvious that nothing short of a total gastrectomy would succeed. This was carried out. The spleen was removed in order to get better access. The duodenum was cut across on a Jones clamp and the duodenal end was inverted. The freed-up stomach, which was still attached to the esophagus, was then brought up and laid out on the chest.

CARCINOMA OF DUODENUM

ONE-STAGE RADICAL PANCREATICODUODENECTOMY, PRESERVING THE EXTERNAL PANCREATIC SECRETION

CASE REPORT

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THE SURGICAL TREATMENT OF CANCER involving the first and second portions of the duodenum, the ampullary region, and the head of the pancreas has recently been receiving an increased amount of attention. The reasons for this lie primarily in the discovery of methods whereby the bleeding tendency in jaundice can be controlled as well as in recent improvements in the pre- and postoperative care of debilitated patients. In view of the effectiveness of these surgical aids it has been possible during the past seven or eight years to change the status of radical pancreaticoduodenectomy from that of a rare surgical feat to one associated with an encouraging incidence of success.

Early in the renewed attack upon this problem efforts were made toward its accomplishment in two stages. The first of these, a cholecystenterostomy, was presumed important in order to control the bleeding tendency which is associated with the jaundice almost invariably present in patients suffering from cancer in and about the head of the pancreas. Early in the annals of the two-stage procedure it became evident that many technical difficulties were involved, particularly with reference to the number of adhesions encountered at the second stage. This, together with a fuller appreciation of the effectiveness of vitamin K in controlling the hemorrhagic tendency led Whipple, in 1940, to perform the first successful single-stage operation. Since then the trend has been definitely toward accomplishing this radical procedure at one operation.

The early history of this type of radical operation, 1900 to 1935, was associated with many unsuccessful efforts directed toward preserving the external pancreatic secretion, a factor presumed necessary to life because it was believed impossible to keep dogs alive following total pancreatectomy. This period was followed by one during the early part of which it was discovered that some patients could survive when deprived of their external pancreatic secretion. At the moment, the question of the absolute necessity of the external pancreatic function is far from finally settled. Apparently, if one is to judge from the reported cases, the state of health of the patients in whom no effort has been made to preserve this function is quite variable, some have shown a remarkable degree of fat digestion, while others have admittedly done poorly, steatorrhea and general debility presenting as a

prominent feature of their postoperative course. Perhaps the most significant single factor is that it is impossible to predict preoperatively which patients will tolerate deprivation of their external pancreatic function and which will not. These factors, together with the appreciation of the fact that pancreatico-enteric anastomoses can be successfully performed provided silk is employed as the suture material, have prompted the recent tendency to secure, if possible, drainage of the pancreas into the gastro-intestinal tract.

Because it has seemed advantageous to counter further the impression, all too generally held, that pancreaticoduodenal cancer is therapeutically hopeless, the following case is added to those already reported. It is that of a patient with carcinoma, primary in the duodenum, in whom a radical pancreaticoduodenectomy was performed in one stage. He survived, relatively free of symptoms, for 14 months, at the end of which period reexploration of the abdomen because of jaundice revealed massive recurrence of the tumor.

Case Report—N.Y.H. No 311583. J. B., white, male, age 57, was first admitted to the New York Hospital in November, 1941, complaining of generalized cutaneous pruritis and of jaundice, both of one month's duration. His family history was irrelevant save that his father died of carcinoma of the stomach. Detailed inquiry into his past history failed to reveal any significant facts prior to the onset of his present illness. Thus the patient dated to approximately four weeks before admission, at which time he suffered from diarrhea for one week. During this his stools became lighter in color, his urine darker, and his skin yellow. Associated with these phenomena, his appetite became poor, he developed generalized pruritis, and lost 20 pounds in weight. On admission, his vital signs were within normal limits and physical examination revealed a well-developed, chronically ill man, who was intensely jaundiced. There were no significant abnormalities noted in the course of his general examination. Interest centered in examination of the abdomen where, in the right upper quadrant, an enlarged liver and gallbladder were palpable. There was no tenderness, nor could any tumor masses be felt.

Laboratory Data (preoperatively)

Blood—Hb, 10 Gm, RBC, 3.8 M, WBC, 9050. Differential normal.

Urine—Negative save for the presence of a marked amount of bile.

Icteric index—110 mg/100 cc.

Stool—Guaiac, 2+.

Prothrombin time—61%, rising to 100% after administration of vitamin K.

Duodenal drainage—Bile absent, indicating complete common duct obstruction.

Secretin test—Marked increase in volume after administration of secretin.

Volume	—501 cc
Bicarbonate	—96 milliequivalents
Total output	—382 (N/10 NaHCO ₃)
Diastase	—673 units per 60'
Trypsin	—115 units per 60'
Lipase	—31,886 units per 60'

Interpretation—These figures are high normal, and fail to indicate any obstruction of the pancreatic ducts.

Blood sugar —78

Blood urea N—11

Roentgenologic Examination—(11/27/41) The stomach, esophagus and duodenal bulb are normal. The second and third portions of the duodenum are very irregular in outline. A mass is noted in the third portion. Chest normal. *Diagnosis* Infiltrative carcinoma of the head of the pancreas. Carcinoma of the duodenum.

Preoperative Course In view of the jaundice, failure to obtain bile on duodenal drainage, the defective appearance of duodenum when visualized with barium as a contrast media, and normal pancreatic function, a diagnosis of carcinoma was made, primary in either the common duct, the duodenum, or the pancreas, and associated with obstruction of the common duct but not of the pancreatic ducts.

Operation—November 28, 1941 Under open drop ether, the peritoneal cavity was entered through a long right upper rectus incision. The liver was found enlarged but without evidence of metastatic involvement. The gallbladder and common duct were hugely dilated. There was a hard tumor mass involving the second portion of the duodenum, the region of the ampulla of Vater, and the head of the pancreas. This was

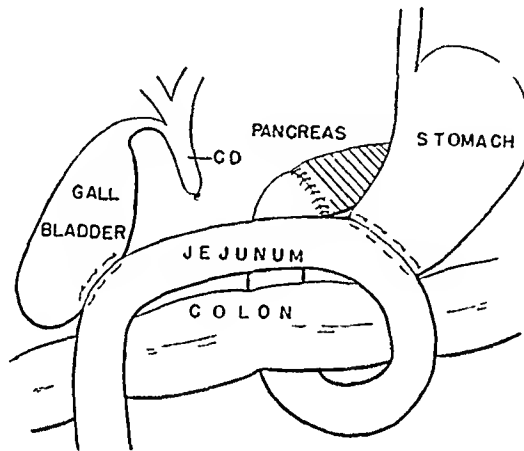


FIG 1—Diagrammatic representation of the reconstruction of the continuity of the gastrointestinal, biliary and pancreatic tracts

freely movable, and resection was undertaken as follows: (1) The right lateral peritoneum was divided as was the gastrocolic ligament, thereby mobilizing the entire duodenum, (2) the common duct was divided, (3) the jejunum was divided just distal to Treitz' ligament, (4) the lower end of the stomach was divided, (5) the pancreas was divided at approximately the junction of its distal and middle third, (6) the tumor and associated structures were then carefully freed from the vena cava and superior mesenteric vessels and removed, (7) reestablishment of the enteric canal and associated organs was accomplished by the following anastomoses: (a) Gastrojejunostomy, end-to-side, (b) pancreaticojejunostomy, end-to-end, (c) cholecystojejunostomy, side-to-side (Fig 1). The wound was closed with through-and-through silver wire and catgut in layers, draining the right gutter through a stab wound in the flank. One drain was placed near the site of pancreaticojejunostomy. Time—five hours.

Pathologic Examination—*Gross* The specimen consists of a segment of duodenum 14.5 cm in length and 6 cm in circumference. The last 5 cm of the duodenum is occupied by a crateriform tumor which surrounds the intestine completely. The ampulla of Vater presents as a lobular mass 2 cm in width and 9 cm in thickness, the orifice admits a 3 mm probe. The common duct above the ampulla is dilated to a circumference of 3.5 cm. The walls are leathery and are invaded by tumor only in the distal portion, where it traverses tumor. The accessory pancreatic duct is patent to the same probe and is not involved in tumor, emerging through duodenal mucosa about 5.5 cm above the ampulla of Vater. The bile-stained head of the pancreas is stony-hard and apparently

shares with the duodenum in its carcinomatous involvement. The duct of Wirsung cannot be demonstrated beyond a small tract which opens near the papilla of Vater in the common duct and runs about 3 cm along its wall, beyond which point a probe will not pass. With the specimen is 11 cm of uninvaded, natural-looking jejunum. As the body of the pancreas is sectioned the main pancreatic duct is identified. By means of a probe this duct can be traced through the substance of the pancreas to emerge at the obstructed ampulla of Vater.

Microscopic examination of the duodenum reveals that there is very poorly-differentiated epithelium growing in a wild and disorderly fashion throughout the thickness of the wall. This epithelium consists of cells which vary considerably in size, shape and staining quality, but are, for the most part, somewhat polygonal. They are arranged in strands and cords and in some places have a tendency to form rudimentary alveoli, which do not contain lumina. A notable feature of these epithelial cells is that many of them resemble mucous cells. Many of them assume the form of "signet rings." Although it is unusual, there is no doubt that this tumor originates in the duodenum rather than in the papillary epithelium, as do the common ampullary tumors.

Postoperative Course—The immediate postoperative course was marred by the development of atelectasis of the right lower lobe, followed by pneumonia. This, however, cleared within a few days upon the administration of sulfadiazine. The abdominal wounds healed without infection, and the drains were removed on the seventh postoperative day, their stab wound closing within the next few days. He was discharged from the hospital upon the 30th day after operation.

During his postoperative period two laboratory studies were of interest. (1) His preoperative fasting blood sugar was 78 mg/100 cc. Immediately following operation this ranged from 120 to 153 mg/100 cc, though at no time was there a glycosuria. On discharge the fasting level was 100 mg/100 cc. (2) The secretin test was repeated, and the values were as follows:

Volume	—175 cc/kg/57'
Bicarbonate	—16 milliequivalents
Diastase	—0.76 units/kg/57'
Trypsin	—0.26 units/kg/57'
Lipase	—104 units/kg/57'

Interpretation This demonstrates the presence of external pancreatic secretion in the gastro-intestinal tract, there being approximately one-sixth of normal function present. In view of the fact that this man manifested no abnormality in fat digestion, it must be assumed either that the collection of the material was far less efficient than in the normal or that one-sixth of the normal amount is adequate for normal digestion of ingested fat. Which of these approaches is correct is of course impossible of determination.

During the first 14 months following operation this man was entirely well save for two attacks of chills, fever, and transient jaundice—interpreted as attacks of ascending cholangitic infection, a phenomenon not infrequently observed following cholecystenterostomy. At the end of this period he again became jaundiced and was readmitted to the hospital.

Physical examination at this time revealed an enlarged liver, upon the surface of which could be palpated several hard nodules. Although the outlook, of course, was not good it was felt that he deserved reexploration in the hope that revision of the cholecystenterostomy could be undertaken and the patient relieved of his jaundice. At operation, under local anesthesia, March 8, 1943, the entire peritoneal cavity was found studded with small metastatic nodules. The anastomosis between the gallbladder and

the jejunum was visualized, and it, too, was the site of numerous metastatic nodules partially occluding the stoma. Microscopic section of the small nodule removed at operation showed recurrent carcinoma.

DISCUSSION—DR ALLEN O. WHIPPLE (New York) My chief objection to this modification is that the common duct is tied off, and the gallbladder is anastomosed to the jejunum distal to the gastro-enterostomy. This means that the chances are more than even that the ligature will cut through the common duct, with a resultant biliary fistula—usually a fatal complication.

A NEW CONCEPT REGARDING THE ORIGIN OF SO-CALLED PRIMARY CARCINOMA OF THE HYPERPLASTIC THYROID*

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THE STRIKINGLY RARE OCCURRENCE of carcinoma in diffuse toxic goiter as compared with its relatively frequent occurrence in preexisting adenomatous goiter excites speculation as to the reason for this wide difference in the incidence of malignancy in these two types of goiter. One may readily believe there is a peculiar reason for the rare discovery of malignancy in exophthalmic or diffuse hyperplastic goiter, particularly in view of the abundant opportunities for pathologic examinations of tissues obtained by resection operations on large numbers of hyperplastic thyroid glands. It appears, at once, that adenomatous goiter is the outstanding culprit in the origin of carcinoma by virtue of its predisposition to malignant degeneration and that the relatively rare coexistence of true adenoma and hyperplastic goiter may, therefore, well be the principal reason for the infrequent occurrence of carcinoma in exophthalmic or hyperplastic goiter. A secondary consideration is the question whether carcinoma in reality ever occurs as a primary lesion in diffuse parenchymatous hyperplasia of the thyroid gland.

In previous reports on malignancy of the thyroid it is repeatedly stated, that carcinoma has not been encountered in the hyperplastic gland of exophthalmic goiter. Thus, Wilson¹ found no instance of malignancy in the hyperplastic gland in a series of 290 patients with malignant tumors of the thyroid observed at the Mayo Clinic. Observations on 55 cases of malignancy of the thyroid by Simpson² accorded with Wilson's findings. However, in more recent writings we find the occasional report of a malignant tumor arising in the hyperplastic gland of exophthalmic goiter, as in the one instance of malignant neoplasm occurring in a series of 90 epithelial malignant neoplasms reported by Coller.³ C W Mayo⁴ stated, on the basis of a study of 737 cases of malignancy of the thyroid, occurring at the Mayo Clinic, that more than three per cent of the cases of adenomatous goiter, in which operation was performed, were malignant, and that approximately 50 per cent of malignant growths of the thyroid were within adenomata. In a subsequent report of 774 instances of malignancy of the thyroid observed in this same Clinic, Pemberton⁵ stated, in agreement with most writers on the subject, that the presence of a preexisting benign adenoma is the most important known etiologic factor in the development of thyroid carcinoma. The association of malignancy and exophthalmic goiter was encountered in ten patients in his series, in four the malignant lesion was confined to an adenoma, and in six

* An abstract of this report was presented at the meeting of the American Association for the Study of Goiter, Rochester, Minn., April 15, 1940.

it developed within the gland itself. Thus, it appeared that in only six instances in the series of 774 malignancies, the malignant lesion occurred in the hyperplastic gland itself. According to previous writers the incidence of malignant tumor arising in preexisting benign adenomata varies between 80 and 95 per cent. In a personal communication, Pemberton stated that the percentage of malignant tumor that arose from preexisting benign adenomata, in his experience, was 87 per cent, calculated on a combined pathologic and clinical basis, but that this figure was subject to errors of interpretation. Welt and Huguennin⁶ stated that in 88 patients with malignancy of the thyroid, 38 had noticed a preexisting goiter for more than eight years, and that in the 50 malignancies occurring without preexisting goiter the evolution of the tumors may have taken several years and may have been carcinoma from the beginning. They stated, further, that carcinoma rarely, if ever, develops in the hyperplastic thyroid of exophthalmic goiter.

Malignancy of the thyroid was found in 52 patients operated upon at the Long Island College Hospital during the ten-year period from 1930 to 1939, inclusive. There were seven instances in which the malignancy occurred in the hyperplastic exophthalmic gland. In four of these malignancy appeared to be primary, at any rate, there was no discernible preexisting adenoma, while in the remaining three the carcinoma definitely had its origin in a coexisting adenoma. In 37 instances the carcinoma arose in adenomatous goiters which were recognized clinically and by pathologic examination.

The suspicion that carcinoma occurring in exophthalmic goiter may have had its origin in an incidental, minute fetal adenoma occurred to the writer ten years ago following the discovery of a small, white, stellate, fibrous nodule, five millimeters in diameter, which occurred in the resected gland from a patient with exophthalmic goiter, and which, upon microscopic examination, proved to be adenocarcinoma. It was, furthermore, noted that the epithelial cells in several areas within the nodule appeared to be of the embryonic or so-called fetal type. It was thought that these cells may well have had their origin in a minute fetal adenoma the identity and recognition of which had been effaced by the multiplication and diffusion of the malignant cells. At any rate, a true encapsulated adenoma was not clearly discernible. During the past ten or twelve years we have been on the lookout for similar lesions in the hyperplastic thyroid gland with the hope that we might be successful in demonstrating that the incipient carcinomata in these instances as a matter of fact, had their origin in true minute fetal adenomata. A minute carcinomatous lesion, definite or strongly suspected, was found in each of nine instances of hyperplastic (exophthalmic) goiter. In three of these we were fortunate enough to discover upon microscopic examination a minute, well-defined and encapsulated adenoma enclosed within the small fibrous nodule, and showing what appeared to be unquestioned carcinomatous degeneration. Practically all the histologic criteria of malignancy, including even the invasion of blood or lymph vessels, were revealed in the sections. The findings in the fourth nodule strongly supported the diagnosis of malignancy.

nancy In three further instances the nodules showed scirrhous carcinoma in which, however, no evidences of a preexisting adenoma were found In another nodule papillary adenocarcinoma was strongly suspected In the ninth case the origin of an adenocarcinoma in a preexisting adenoma was suspected because of the appearance of the cells enclosed within the lesion These were definitely of the embryonic so-called "fetal" type Finally, passing mention may be made of unquestioned adenocarcinoma arising in a minute adenoma occurring in an otherwise normal gland Naturally, a considerable number of lesions proved to be of simple benign nature, and resembled those to which Graham⁸ has drawn attention

The material forming the basis for the present study consisted of blocks of tissue cut from the resected specimens of hyperplastic (exophthalmic) goiter in such a manner as to incorporate in their centers the minute whitish nodules suspected of malignancy and previously described in the introduction Tissues were fixed in formalin and Zenker's solutions and sections prepared, in serial manner, at frequent levels in order to be representative of the detailed histopathology in all parts of the lesion Sections were stained with hematoxylin and eosin for general histology and, after the Pappenheimer methyl-green pyronine method, described by Mallory,⁹ for the demonstration of plasma cells

It is our purpose to report in detail the gross and microscopic findings in two cases of exophthalmic goiter in each of which a minute carcinomatous lesion, measuring 0.5 cm. in greatest diameter, was found to enclose a circumscribed and encapsulated adenoma, which had undergone malignant degeneration and which was shown to be the point of origin of the malignant lesion These findings together with those observed in seven further, proved or suspected, instances of minute incipient carcinomata occurring in the hyperplastic thyroid will be considered in the discussion and summary In one of these seven cases, the origin in adenoma was demonstrated, and in three such origin was strongly suspected It is hoped that these findings will aid in establishing the fact that primary carcinoma rarely, if ever, occurs in the hyperplastic thyroid gland and that when carcinoma does occur its origin in a minute adenoma has been obscured by the overgrowth of the lesion The findings are intended, further, to establish the classification of primary or secondary carcinoma in hyperplastic goiter

CASE REPORTS

Case 1—D. J., female, age 24, was first seen January 5, 1937, at which time she complained of symptoms of hyperthyroidism of four months' duration Upon examination she showed exophthalmos and a diffuse moderate fullness of the thyroid gland which exhibited thrills and bruits at the poles Cardiac action was accentuated and the pulse was 146 The basal metabolic rate was +74 per cent, and after preparatory treatment of the patient with Lugol's solution it had declined to +24.6 per cent above the average normal The preoperative diagnosis was exophthalmic goiter with marked hyperthyroidism

Operation—Double lobectomy was performed on January 18, 1937

Pathologic Examination—Gross The resected thyroid gland had the usual colloid appearance of hyperplastic goiter after the administration of iodine. Both the gross and microscopic appearances confirmed the diagnosis of hyperplastic goiter. The resected portion of the right lobe was cut longitudinally, whereupon a small whitish, indurated nodule, measuring 0.5 cm in greatest diameter, was exposed. In the center of the lesion there was a minute nodule, which measured 2 mm in diameter, and which was surrounded by a narrow zone of fibrous reaction. Tentatively, this whitish lesion was considered to be carcinomatous. A block of gland comprising the lesion and a generous area of surrounding thyroid was cut from the specimen and prepared for sectioning.

Sections were cut in serial fashion at frequent intervals beginning with the most superficial portion of the lesion. The findings in four sections at different levels (Fig 1, A, B, C, D) are reported.

Microscopic Description—Low Power Section A (Fig 1) represented a section through the superficial portion of the lesion. In the center of the section was a discrete, rounded, well-defined and encapsulated nodule, which measured approximately 1 mm in diameter. This nodule was composed of densely blue-staining, tortuous cords of cells with dark staining nuclei and without definite acinous structure. No colloid was visible. In one zone, comprising approximately one-third of the nodule, there were irregular clear areas composed of hyalinized connective tissue in which remnants of acinar epithelium were seen. In another area numerous small masses of blue-staining calcium granules were noted. Immediately surrounding the nodule there was a wide zone of compressed lobular gland composed of minute acini containing droplets of colloid. Further peripherally there was a large area of dense hyaline pink-staining fibrous tissue, in the meshes of which there were cellular accumulations. Radiating strands of connective tissue arising from this hyalinized area were seen penetrating the surrounding normal appearing gland. There was a gradual transition from the irregular, diffusely cellular areas to the surrounding normal appearing gland.

High Power The interior of the central nodule was composed largely of wavy, papillary columns of compact lining cells containing large, deeply-staining nuclei. There was no tendency to the formation of normal acini. The low columnar cells lining the cords were often arranged in reduplicated layers. The nuclei of these cells were mostly large, rounded, oval and irregularly shaped, with the long axes perpendicular to the basement membrane. They were hyperchromatic, deeply-staining and many of the smaller ones were densely pyknotic. The stroma between these cords was scant. Between the cords infiltrated cells of various types including lymphocytes, polymorphonuclear epithelioid and a few plasma cells were seen. In addition to the rather definite papillary cords there were also large groups of well-defined cells with huge hyperchromatic nuclei.

Adjoining the area of papillary cord formation was another area of numerous closely aggregated cells with large, rather pale nuclei and with a scant vacuolated protoplasm. These cells gave the impression that they were undergoing degeneration. There was no definite structural arrangement. Scattered through this area, furthermore, were numerous masses of calcium granules. A third area within the nodule was composed largely of hyalinized connective tissue containing few nuclei and remnants of more or less well-defined acinar lining cells, many of which were atrophied and degenerating. Here, also, several masses of calcium granules were seen. No colloid was apparent anywhere in the nodule.

The thin capsule of the nodule was composed of broad concentric bands of hyalinized fibrous tissue in which there were relatively few nuclei of various sizes and shapes. Immediately outside of and adjoining the capsule there was a relatively large zone of anastomosing bands of connective tissue, in the spaces of which there were small compressed thyroid acini which appeared atrophic and practically without colloid. In addition, in these spaces there were masses of cells of every description. Some cells had huge, pale-staining rounded nuclei, while others contained nuclei irregular in shape,

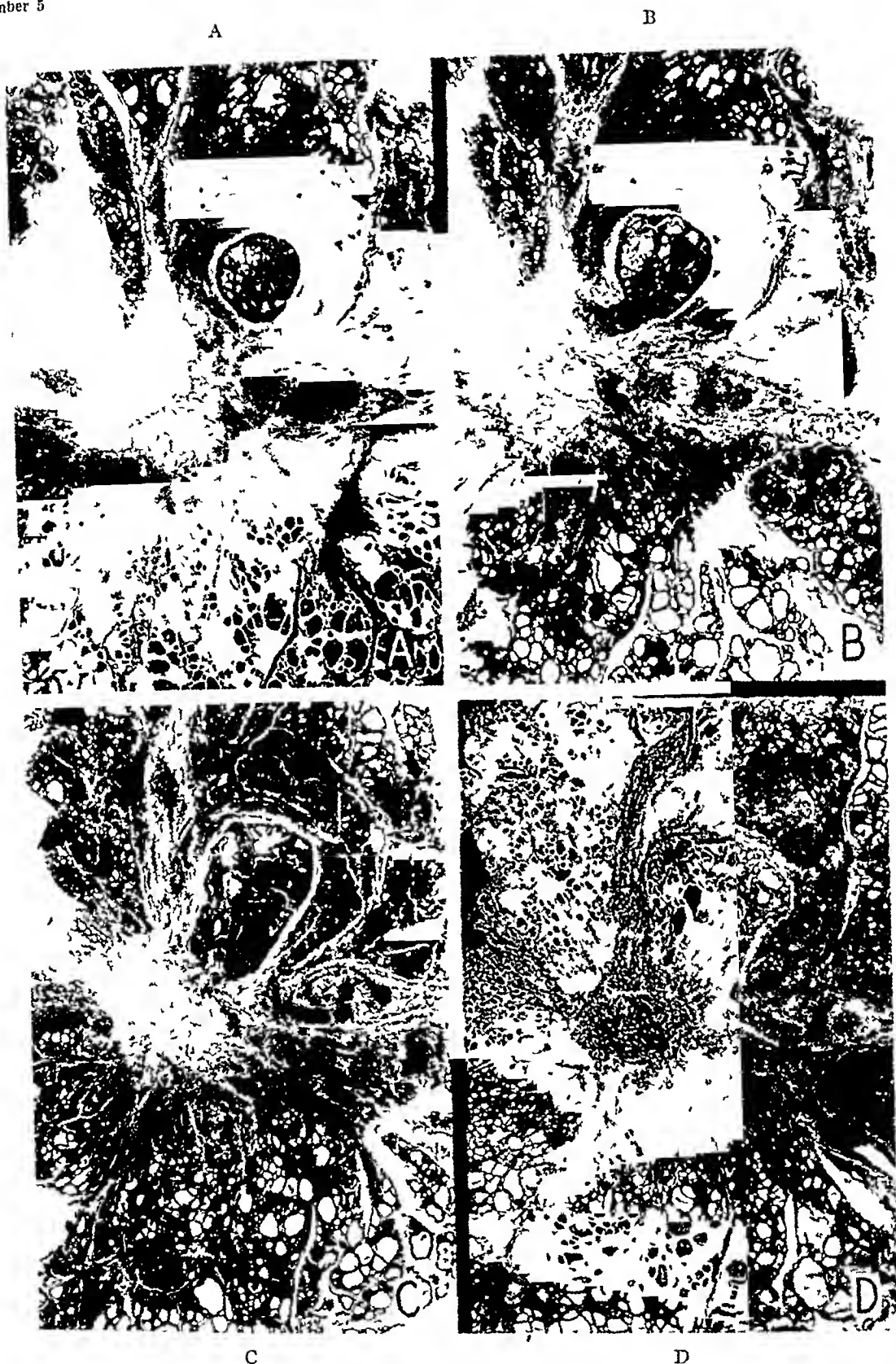


FIG 1—Case 1 Photomicrographs ($\times 12$) of four representative sections at different levels in a small scirrhous carcinoma occurring in exophthalmic goiter. Note in the center of the lesion a minute adenoma, the site of the primary papillary adenocarcinoma which had perforated the capsule of the adenoma.

A Superficial section of the encapsulated adenoma and the surrounding scirrhous carcinoma.
B Section at a deeper level showing perforation of the capsule by the papillary neoplasm which is extending beyond the confines of the adenoma.

C The section at this level shows a large defect in the capsule and the hyalinized fibrosis opposing the extension of the malignant growth.

D Section showing the wide area of scirrhous carcinoma and in its center the papillary primary neoplasm still confined to the adenoma.

densely stained and often pyknotic and shriveled in appearance. These cellular masses showed no definite glandular structure and loosely aggregated cells were often seen filling what appeared to be lymphatic and vascular spaces. Numerous lymphocytes in small aggregations, large numbers of plasma cells and occasionally polymorphonuclear cells were seen. Finally, peripheral to this area of fibrous reaction there was a wide zone of dense cellular infiltration without definite architecture and composed of large cells with hyperchromatic, oval, irregular nuclei, some of which showed chromatin figures. Surrounding groups of these large irregular cells, lymphocytes and plasma cells in large numbers were recognized. By gradual transition this infiltrated cellular zone finally assumed the appearance of the contiguous normal exophthalmic gland.

A second section (Fig 1, B), which illustrated the appearances at a deeper level in the lesion, showed the following histologic findings:

Low Power. The central nodule presented appearances in many respects similar to those just described for Section A. The striking finding, however, was the opening in the capsule through which a dense stalk of tissue, composed of cellular epithelial cords, was seen extruding itself and invading the surrounding tissue which showed an extreme hyaline fibrosis. In general the findings in the zone of reaction in the gland surrounding the nodule were much the same as those described for Section A.

High Power. A large opening in the capsule of the nodule was seen through which protruded a thick column composed of cellular epithelial cords. Between the cords could be seen a small amount of stroma containing numerous lymphoid, plasma and epithelioid cells. The cords were lined by low columnar cells, the nuclei of which varied greatly in size and shape. Some were huge, some small and oval in shape, while others were distorted and pyknotic. Colloid-containing acini were not apparent. Closely adjacent to the lesion these cords became separated into ill-defined islands of epithelial cells by the penetration of strands of hyalinized fibrous tissue in the spaces of which masses of large, hyperchromatic nuclei of cells without any definite arrangement were seen. Surrounding the nodule there was a wide zone of small ill-defined thyroid acini practically devoid of colloid. Numerous lymphocytes and plasma cells were seen between the acini. Apposing the point of perforation of the nodule there was a large area of hyalinized fibrous tissue in the spaces of which were seen irregular masses of cells consisting of large epithelial cells with huge hyperchromatic nuclei, lymphocytes and numerous plasma cells. From this hyalinized fibrous zone strands of connective tissue radiated outwards into the more normal appearing thyroid parenchyma.

A third section, representative of appearances at a still deeper level in the nodule (Fig 1, C), revealed the following findings:

Low Power. The nodule at this deeper level was still well-defined and encapsulated but larger and more oval than in the previous sections. In general, it had the appearance described for the previous section (Fig 1, B). It was composed of wavy, cellular cords, many of which were arranged in approximately parallel rows. There was a zone of dense hyaline connective tissue reaction around the cellular tissue extruded through the rent in the capsule. From this dense zone of fibrosis, radiating strands of connective tissue penetrated the surrounding more normal appearing gland. Large cellular aggregations without definite structure were seen between these radiating strands of connective tissue.

High Power. The capsule of the nodule was well-defined and made up of concentric layers of hyaline connective tissue containing moderate numbers of flattened nuclei. The nodule was composed of several large, irregular acini, many small acini and numerous parallel cords of epithelial cells. The lumina of the largest acini contained a granular pale-staining colloid in which could be seen numbers of fibroblasts, some free epithelial cells and a few lymphocytes. In some areas the colloid seemed to have undergone organization, as definite pink-staining fibrous tissue was recognized. The acini and cords throughout were lined by low columnar cells with oval nuclei which were closely

CANCER OF THE THYROID

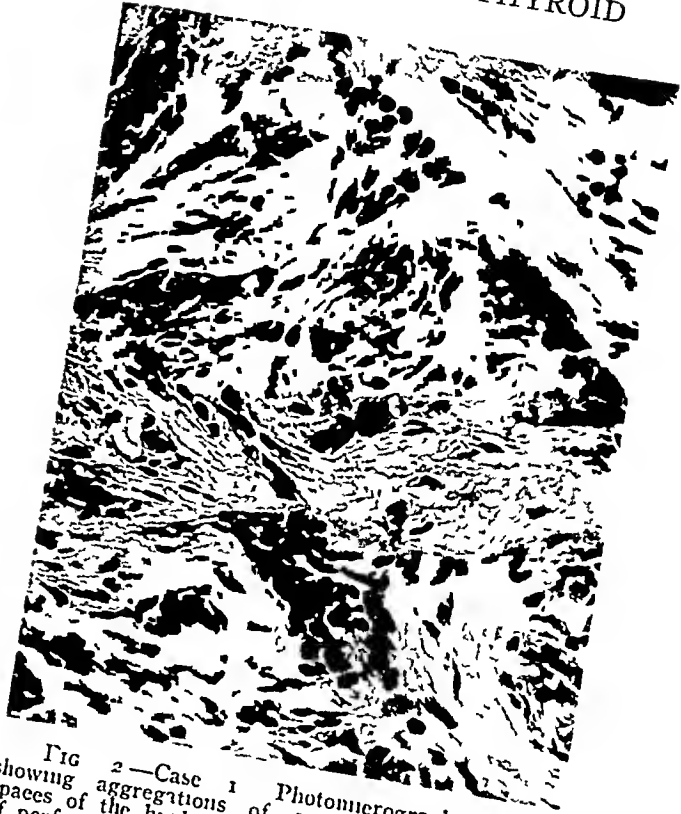


FIG 2—Case 1 Photomicrograph ($\times 300$) showing aggregations of epithelial cells in the spaces of the hyalinized fibrous tissue at the point of perforation of the adenoma. The cells and their nuclei varied greatly in size, shape and general character, and definite mitotic figures were noted (See Fig 3)

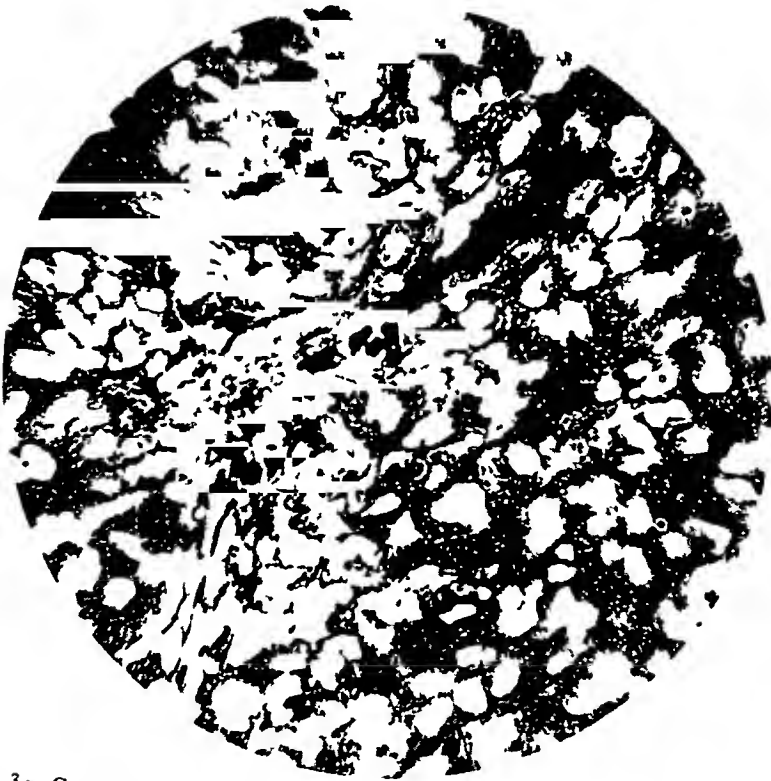


FIG 3—Case 1 Photomicrograph ($\times 450$) showing the variation in size, shape and chromatin content of the malignant cells enclosed in spaces of the fibrous stroma illustrated in Figure 2. Note the mitotic figure in the center

assembled, deeply-staining and rich in chromatin. In some areas the lining cells were reduplicated. A minimum amount of stroma was seen. Here and there small masses of calcium were noted. The nodule was surrounded, except at the point of perforation, by a zone of densely packed small acini, between which one could recognize groups of lymphoid cells, plasma cells and occasional polymorphonuclear leukocytes. In some areas acinar formation was ill-defined. The findings in the zone of reaction adjacent to the point of perforation of the nodule were not unlike those described for the previous two sections (Sections A and B), except that the cellular infiltration was even more irregular and diffuse and was demarcated into islands by strands of hyalin connected tissue (Fig 2). The epithelial cells aggregated in these islands were of every conceivable size, shape and general character. Many huge pale-staining nuclei containing granular chromatin were seen, while the nuclei in other instances were shrunken, shriveled and pyknotic. Definite mitotic figures were present (Fig 3). Intermingled with

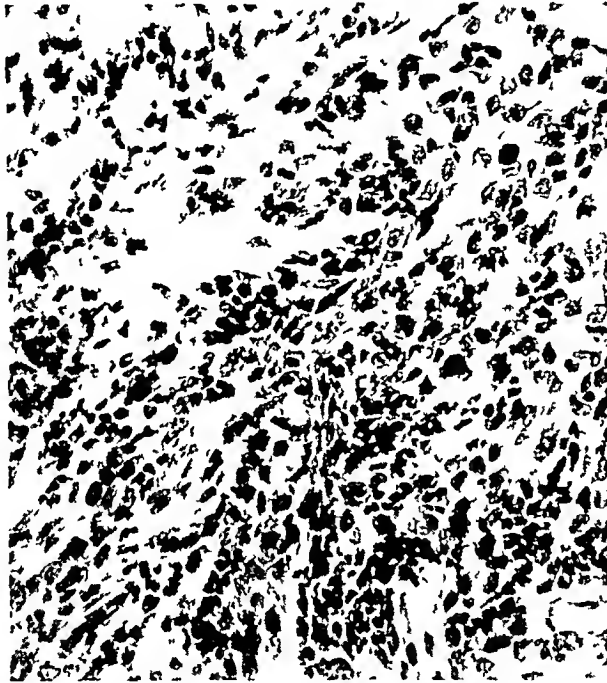


FIG 4—Case 1. Photomicrograph ($\times 300$) illustrating the appearance of the cellular conglomerates in the meshes of the fibrous tissue reaction about the adenoma. Large numbers of epithelial cells with hyperchromatic nuclei and of varying size and shape together with lymphocytes, polymorphonuclear and plasma cells were noted.

these epithelial cells, groups of lymphocytes, plasma cells and occasionally polymorphonuclear cells were seen. The strands of hyalin connective tissue radiated outwards and penetrated the adjacent relatively normal appearing gland. Between these strands of connective tissue there were dense cellular accumulations consisting of large epithelial cells with large irregular nuclei, lymphocytes and plasma cells. Here, again, occasional mitotic figures were seen.

A fourth section (Fig 1, D) showed, deeper in the lesion, appearances as follows:

Low Power. At this deeper level the microscopic section indicated that the nodule was larger and less well encapsulated than in the more superficial sections previously described. About one-half of the circumference was in immediate contact with a large hyalinized zone of fibrous tissue while in other respects the findings were similar to those in the previous sections already described.

High Power. A more decided branching of the cellular cords was noted. The

stroma between the cords had a myxomatous appearance and contained elongated spindle-shaped fibrillar cells and numerous small congested capillaries. In other areas the stroma between the cords of cells contained an abundance of plasma cells and lymphocytes. Polymorphonuclear cells were infrequent. There was an intense hyalin connective tissue reaction around the nodule. The meshes of this tissue contained groups of conglomerate epithelial cells without definite arrangement and with hyperchromatic nuclei of varying size and shape (Fig 4). Between the larger cells there was an infiltration of plasma cells, lymphocytes and polymorphonuclear cells. Some of these spaces, giving the impression of vascular or lymphatic spaces, were crowded with large epithelial cells. Small masses of chromatin granules were recognized suggesting karyorrhexis. A wide zone of cellular infiltration extended from the nodule into the surrounding more normal appearing gland.

Pathologic Diagnosis Small scirrhous carcinoma occurring in exophthalmic goiter and secondary to papillary carcinoma originating in a minute adenoma, the capsule of which had been perforated by the malignant neoplasm.

Comment—The carcinomatous lesion in this case might readily be considered primary in hyperplastic goiter had it not been for the discovery of a minute encapsulated adenoma in the center of the growth. The malignant degeneration of the adenoma had involved and perforated the capsule and begun to invade the surrounding thyroid parenchyma. In the further overgrowth of the lesion the true origin in adenoma would have been obscured and the diagnosis of "primary carcinoma not arising in adenoma" would have been a natural one.

Case 2—G. M., male, age 40, was first seen March 8, 1938, when he complained of symptoms of hyperthyroidism of six weeks' duration. His outstanding complaint was fatigue. A unilateral exophthalmos, tremor, and evidences of marked loss of weight were noted. The thyroid gland was moderately enlarged and showed mildly

positive vascular signs at the poles. The pulse was 96, and the basal metabolic rate after the period of preparation with iodine, was 20 per cent above the average normal. The preoperative diagnosis was exophthalmic goiter with moderate hyperthyroidism.

Operation—Double lobectomy was performed March 23, 1938.

Pathologic Examination—*Gross* The resected thyroid gland gave the appearance of increased colloid content characteristic of the hyperplastic thyroid gland after the administration of iodine. The preoperative diagnosis of hyperplastic goiter was verified after study of the microscopic preparations. Section through the left lobe near its inferior pole disclosed a small, firm, whitish lesion, about 0.5 cm in diameter (Fig 5). The surface of this lesion presented a stippled appearance, and minute strands of fibrous tissue were seen radiating in stellate fashion outward from the lesion. The gross ap-



FIG 5—Case 2. Photograph of the resected left thyroid lobe in a case of exophthalmic goiter. Note the white nodule, 0.5 cm in diameter, which proved to be a typical scirrhous carcinoma. In the center of this lesion a minute adenoma, 1 mm in diameter, was found to be the site of a papillary adenocarcinoma, which thus proved to be the primary lesion.



FIG 6—Case 2 Photomicrographs ($\times 12$) of sections of scirrhous carcinoma occurring in exophthalmic goiter and secondary to a primary malignancy of a minute adenoma

A Section through the center of the adenoma and the surrounding scirrhous carcinoma showing, on the right, perforation of the capsule and the adjoining area of papillary carcinoma while to the left an area of scirrhous carcinoma borders on the nodule. Note the central necrosis in the adenoma and the subcapsular darker zone of calcium deposit

B Section at a deeper level

C Section through the very periphery of the nodule, the capsule of which is still recognizable as a central area of fibrous tissue. Note the large area of papillary carcinoma which had overgrown the primary nodule

CANCER OF THE THYROID

pearance suggested the possibility of malignancy. A block of gland including the whitish nodule was cut from the specimen. Microscopic sections, cut in serial fashion, were then prepared in the usual manner. Three representative sections from different depths in the lesion and beginning at approximately its middle were chosen for detailed report of the microscopic findings.

Microscopic Description—Low Power. Section A (Fig 6) through the center of the lesion, showed a rounded, encapsulated nodule, slightly over 1 mm in diameter, which was embedded in a zone of dense hyalinized fibrous tissue. The interior of the nodule was composed largely of a lightly pink-staining, degenerated, semihomogeneous tissue in which the outlines of large and small acini were visible as empty-appearing spaces, the lining walls of which showed occasional small atrophic nuclei. These spaces



FIG 7—Case 2. Photomicrograph ($\times 85$) of a section including the margin of the adenoma (Fig 6, A) with its capsule and the adjacent extracapsular area of papillary carcinoma. Note the papillary cords of low columnar cells in poorly defined acinous formation and, on the left, the necrosis within the adenoma.

doubtless represented the lumina of former acini. Surrounding this area of degeneration and immediately under the capsule of the nodule there was another well-defined zone of pink-staining ground substance in which were seen deeply blue-staining granular deposits of calcium. The nodule was enclosed in a well-defined capsule of hyalinized fibrous tissue and at one pole the capsule was extremely thin and gave the appearance of having been perforated. Adjacent to this point of apparent perforation there was a wide area of large and small anastomosing bands or septa of hyalinized connective tissue enclosing acini which were irregular in size and which showed numerous papillary infoldings of the lining cells. At the opposite pole the adenoma was partially surrounded by a dense zone of homogeneous hyalinized fibrous tissue, in the small lacunae of which accumulations of cells without particular arrangement were seen.

High Power In the high power magnification, the adenoma showed a relatively large central area of degenerated, lightly pink-stained ground substance in which irregular empty spaces of varying size were seen. The lining walls of these spaces showed an occasional atrophic nucleus, and gave the definite impression of being the remnants of former thyroid acini. Normally staining thyroid tissue was not found within the nodule. Immediately under the capsule of the adenoma there was a fairly wide zone composed of fine hyalinized fibrils, in the meshes of which an abundance of blue-stained granules of calcium were seen. The thick capsule was composed of concentric layers of dense hyalin connective tissue containing only occasional atrophic appearing nuclei. Adjacent to the nodule at the point of thinning and evident perforation of the capsule, there was a large irregular area of anastomosing bands of hyalin fibrous

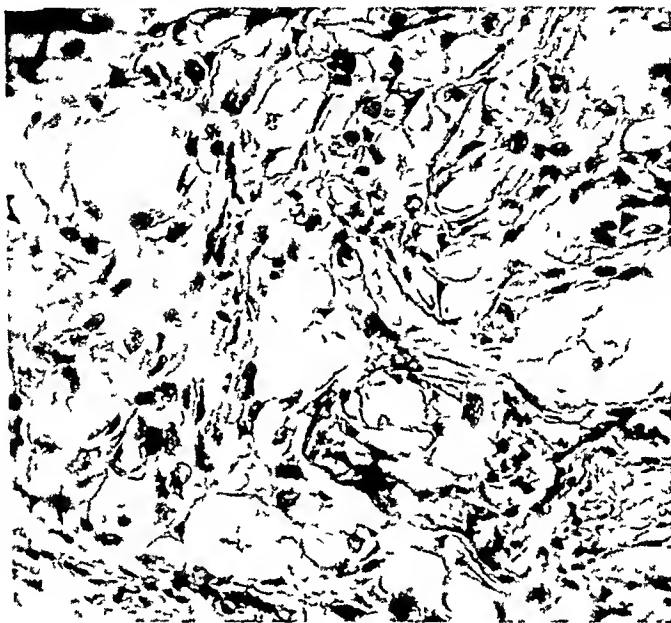


FIG 8—Case 2 Photomicrograph ($\times 300$) of the papillary carcinomatous area adjacent to the adenoma (Fig 6, A) and illustrated in Figure 7. Note the variation in shape and size of the hyperchromatic nuclei and the complete lack of glandular architecture. The protoplasm of the cells is scant in amount and irregular masses of chromatin are seen in the nuclei.

tissue enclosing irregular small and large acini many of which showed papillary projections of the lining walls (Fig 7). The lining cells were low columnar or cuboidal, their protoplasm was granular and contained nuclei some of which were large and palely-stained while others were small, shrunken, irregular in shape and deeply stained. Occasional reduplication was seen. Some of the acini contained a thin granular colloid which was crenated, or vacuolated, while others contained a minimal amount of granular colloid and a few desquamated cells. In some of the smaller connective tissue spaces groups of large cells with scant protoplasm and irregularly shaped hyperchromatic nuclei were noted. These cells lacked definite arrangement. In one rather large area there was a great diversity in shape and size of the hyperchromatic nuclei and there was complete lack of normal glandular architecture (Fig 8). The protoplasm of the cells was scant and occasional nuclei contained irregular chromatin masses but definite mitotic figures were infrequent. In one area, between the lesion and the adjoining normal gland, there was a focal area of infiltration of lymphocytes, plasma cells and a few polymorphonuclear cells. From the margin of the lesion, connective tissue strands were seen radiating into the adjoining normal hyperplastic gland. There

was no clear line of demarcation between the evidently malignant lesion and the normal gland. In many areas at the periphery of the lesion, there were groups of cells lying in what appeared to be lymph spaces or veins.

Section B (Fig 6), from a level deeper than in Section A, showed in both the low and high power magnifications many of the features already described for Section A. The adenoma now was more rounded and the capsule was more clearly defined, particularly in the zone of perforation previously described. Increased calcium deposits were noted in the capsule at this point. The large central area of necrosis surrounded by the zone of calcium deposit was still visible. A strikingly wide zone of hyalinized fibrous tissue surrounded the nodule. Many bands of intertwining connective tissue enclosed small and large spaces containing groups of epithelial cells without definite structure and small irregularly formed acini. In the larger spaces one could see thyroid acini of irregular size and shape some with papillary infoldings of the walls. In many instances there was a reduplication of the lining cells. In one large area there was an abortive attempt to form acini. The nuclei of the epithelial cells were of every size and shape some containing a scant amount of granular chromatin while others were definitely rich in chromatin or pyknotic (Figs 7 and 8). In a few instances there were lymphoid and plasma cell accumulations about the epithelial cells imbedded in the connective tissue ground substance. More peripherally, a zone of invasion was recognized in which cords and masses of epithelial cells were seen between connective tissue strands which radiated outwards into the adjacent normal gland.

Section C (Fig 6), illustrated the findings at a level still deeper than that described for each of the two previous sections. A mere vestige of the primary adenomatous nodule was still recognizable in the central area of calcium deposit enclosed in fibrous tissue. This section passed tangentially through the very periphery of the nodule and, in both the low and high power magnifications, resembled the appearances described for Section B, with the exception that the spaces enclosed in the broad bands of hyaline connective tissue were larger and the contained thyroid tissue was more papillary in structure. There were large irregular acini filled with colloid while others contained granular detritus. The cells lining the acini were of the low cubical type and showed shrunken cytoplasm. The nuclei were strikingly large, irregular in shape, hyperchromatic, often reduplicated and in certain areas there was desquamation of the lining cells into the lumina. Another rather large space in the hyaline stroma was occupied by cells irregularly grouped with scant protoplasm and containing nuclei varying greatly in size and shape. In general, the findings were not unlike those described for Section B.

Pathologic Diagnosis Scirrhus and papillary adenocarcinoma, occurring in exophthalmic goiter and arising in a papillary carcinoma which was primary in a minute adenoma. Perforation of the capsule of the adenoma by the malignant lesion.

Comment—The scirrhus and papillary adenocarcinoma occurring in this case of exophthalmic goiter had its origin in a papillary carcinoma which was primary in a minute adenoma. The adenoma had undergone almost complete degeneration. The malignant growth after perforating the capsule of the adenoma had involved the adjacent hyperplastic gland. The scirrhus nature of the growth was readily recognized. Again, except for the fortuitous finding of the adenoma, a diagnosis of carcinoma primary in the hyperplastic exophthalmic gland would have been justified. A follow-up report, dated July 20, 1943, approximately five and one-half years after thyroidectomy, indicated that the patient was in excellent health.

DISCUSSION AND SUMMARY

Nine instances of minute carcinomatous lesions occurring in the diffuse hyperplastic thyroid gland have been carefully studied. The pathologic findings revealed that in three instances, two of which are reported in detail, the lesions were definitely not primary in the hyperplastic gland. They were unmistakably secondary to minute fetal adenomata, and presented all the histologic criteria of malignancy. In several of the remaining cases, the lesions, because of the embryonic character of their epithelium, were strongly suspected of having originated in adenomata. It would appear that carcinoma, even in the relatively rare instances in which it occurs in the hyperplastic thyroid, originates in a preexisting minute adenoma. The question, therefore, arises whether carcinoma is ever truly primary in the hyperplastic thyroid gland.

There are two commonly stated theories concerning the origin of these minute adenomata. According to the first, propounded by Wolfer,⁷ and in accordance with the Cohnheim theory of the origin of tumors from congenital "anlagen," the adenoma was thought to arise from the round glandular cells which Wolfer described as occurring in irregular groups both in the thyroid of the newborn and that of the adult. Wolfer believed that they must be considered as embryonal glandular cells which have not been utilized in the formation of the normal thyroid follicles and thus became interacinar in position. He stated, further, that in the highly organized thyroid gland with completely developed acini and high columnar epithelium such interacinar cell groups are usually not discernible. Thus, he thought it was probable that in these instances the undifferentiated cell groups are regularly organized and converted into normal glandular acini. Accordingly, it would seem that the potential of hyperplastic development has exhausted the available undifferentiated cells. Hence, there are no remaining cell groups capable of development into future adenomata. This, on theoretic grounds, could explain the rare coexistence of adenoma and exophthalmic goiter. The second view was expressed by Graham,⁸ who, by argument and exclusion, came to the conclusion that, by dedifferentiation or reversion of the follicular cell, a more embryonic type of thyroid epithelial cell from which the adenoma probably arises, is formed. The influences which would cause the thyroid cell to dedifferentiate after its differentiation to the highest functional stage of hyperplastic cell of exophthalmic goiter remain obscure.

I should like to offer the theory that the true adenoma probably has its origin in certain cells which occur in the normal and hyperplastic follicle, and which are known to have the characters of fetal or embryonic cells. They are not uncommonly found singly or in pairs and are interposed between the follicular lining cells of the hyperplastic gland. They can be clearly differentiated from the remaining cells of the follicle by their differences in size and shape and in the nature of the mitochondria which their protoplasm contains. They differ in that they have a rich content

of mitochondria which are rounded, short filamentous or granular, and resemble fetal or embryonic cells, whereas in the hyperplastic cell of exophthalmic goiter the mitochondria are long filamentous or spirilliform and fewer in number. Inasmuch as these follicular "fetal" cells are similar in appearance to the cells of the fully developed fetal adenoma they may readily be the ancestral cells of this tumor. According to this view, it is unnecessary to presuppose the dedifferentiation of the highly developed follicular cell. It seems plausible that the follicular "fetal" cells might well predispose to development of carcinoma either primarily or through the intermediate stage of a benign adenoma.

The exciting stimulus for the initial development of cancer either by dedifferentiation of hyperplastic follicular cells or from the fetal-type follicular cell is, of course, totally obscure. One wonders whether carcinoma ever originates in the hyperplastic cell. From the results of studies here reported, it would seem that the hyperplastic cell is probably rarely if ever subject to true malignant degeneration. The undifferentiated fetal cell in contrast to the more highly differentiated hyperplastic cell would seem definitely less removed from a predisposition to malignancy.

It is a common observation that the coexistence of true adenoma and the hyperplastic gland of exophthalmic goiter is strikingly rare. This fact doubtless accounts for the extremely low incidence of carcinoma in exophthalmic goiter. It may well be that even in the few reported cases of malignancy in hyperplastic goiter the malignant neoplasm may well have had its origin in a minute adenoma. In recognized clinical carcinoma involving exophthalmic goiter, it would be impossible to demonstrate the adenomatous origin of the neoplasm because the original adenoma would long have been obscured by the overgrowth by the malignant process. Accordingly, carcinoma arising in a minute adenoma might readily be erroneously considered as primary in the hyperplastic gland. In view of the difficulty in determining the primary tissue, one can never be quite correct in classifying certain specific instances of carcinoma of the thyroid as "adenocarcinoma not arising in adenoma."

The adenoma is essentially an abortive attempt to form normally differentiated tissue. In failing to accomplish this its cells tend to remain fetal in type and the adenoma continues as a precancerous lesion and as an intermediate stage between the original fetal cells and eventual malignant degeneration. The adenoma may grow to a considerable size as a benign tumor and later become malignant, or, as these studies reveal, it may be malignant from its earliest period when virtually submicroscopic in size.

Incidentally, the present study illustrates the futility of supposing that a truly early diagnosis of carcinoma could be made, because there is evidence that these predisposing lesions which are so small as to be easily overlooked in routine examinations of the excised gland, in reality probably have existed for a long time. This idea is borne out by the dense

fibrosis and even partial calcification seen in a number of the lesions studied. It is interesting to speculate what might have been the outcome had the patients with these lesions described not been operated upon. It would seem that there are many instances in which eventual carcinoma arising in a minute adenoma is prevented by the commonly practiced surgical resections.

CONCLUSIONS

(1) Evidence is submitted indicating that carcinoma apparently primary in (exophthalmic) hyperplastic goiter is, in fact, secondary to malignant degeneration of an intermediate preexisting minute adenoma. It is probable that carcinoma is rarely, if ever, truly primary in the hyperplastic thyroid gland.

(2) Nine instances of incipient carcinomatous lesions occurring in the diffuse hyperplastic thyroid were studied. Pathologic findings revealed that in three of these cases, two of which are reported in detail, the carcinomatous nodule showed a central minute cancerous adenoma. In several of the remaining cases, the origin of the malignant lesions in preexisting minute adenomata was strongly suspected.

(3) The concept of primary carcinoma occurring in the hyperplastic thyroid is not based on firm premises and is likely incorrect.

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CARCINOMA OF THE BREAST*

II—CRITERIA OF OPERABILITY

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WE HAVE RECENTLY PRESENTED¹ in detail the results of treatment in a series of 1040 cases of carcinoma of the female breast seen at the Presbyterian Hospital in New York during the period 1915 to 1934 (inclusive)

In the course of studying this series of cases we were impressed with the frequency with which radical mastectomy had been performed upon far advanced cases, cases which we ourselves today would classify as inoperable. Several of the surgeons who performed many of the operations in the series held to the theory that patients should be given their chance of cure by operation, even though it might be exceedingly small. The practical application of this theory led them to attempt to remove very extensive lesions. This fact makes the series of cases particularly instructive to study from the point of view of determining just which of the various clinical signs of locally advanced carcinoma of the breast are truly indicative of incurability, or to speak more correctly, of inoperability, for operation is the only method by which we can cure breast carcinoma.

In this, as well as in other clinics, there is strong evidence that the improvement in the results of radical mastectomy which has occurred during recent years is due to a large extent to the narrowing of the limits of operability. We are gradually learning that certain types of cases can not be cured even by the most radical operation. But this problem of estimating the true extent of breast carcinoma and of accurately classifying the cases from the clinical evidence alone is a difficult one. We need more detailed data based upon careful and complete clinical descriptions of the disease picture. In studying the Presbyterian Hospital series of cases we have made a special effort to provide these data. The comparatively complete case histories available in this hospital favored this effort, and the good follow-up provided the necessary information as to end-results of operation. The use of the punch-card method of analyzing our data has made it possible to determine the statistical significance as regards operability of the various clinical signs of the extent of the disease, not only individually but in various combinations. A large series of correlations between clinical signs and end-results was easily worked out by this method, and in the present communication we shall present such of these correlations as seem interesting and significant. Miss Dorothy Kurtz, Supervisor of the Presbyterian Hospital Record Room, and an authority on the use of the punch-board method in medical problems, has advised and assisted us in this study.

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Reference to our recent communication dealing with results of treatment in the Presbyterian Hospital series of cases will show that 640, or 61.5 per cent of the total of 1040 patients with breast carcinoma seen in the hospital over the period 1915 to 1934 (inclusive), were treated by radical mastectomy. Within the first five years following operation 146, or 22.8 per cent of these patients developed local recurrence. At the end of this period 231, or 36.1 per cent, remained free of clinical evidence of carcinoma and were classed as five-year clinical cures.

In the following pages 21 different factors are examined *separatim* which have been presumed to be evidences of unfavorable prognostic significance and which were present in women treated by radical mastectomy. In each instance the five-year clinical cure rate is compared with that for the group as a whole. It will be shown that in the case of eight different factors radical operation invariably failed to cure a single case. These factors we consider mandatory contraindications to radical mastectomy. Five other factors, not by themselves categorical contraindications, will be shown to become so when more than one of them is present in the same patient. Finally, it will be shown that some factors popularly supposed to be of very grave import are not as black as they have been painted. Constitutional factors will be considered first, followed by those which may be classified as physical signs of the extent of the disease.

CONSTITUTIONAL FACTORS AFFECTING OPERABILITY

At some future date, when we know much more than we now do about the relationship of somatic type to disease, it may be possible to correlate a variety of constitutional factors with the outlook in breast cancer. Today, however, we are limited to reporting the effects of more prosaic factors such as age and pregnancy-state upon prognosis.

AGE OF THE PATIENT

The most obvious of these constitutional factors is the age of the patient. It has long been recognized by oncologists that neoplastic disease in general is apt to be more malignant when it occurs in young persons. This relationship has been confirmed in breast cancer by many observers, and Taylor² has emphasized it in a separate communication on the question. Some surgeons go so far as to decline to operate upon women under the age of 30 who develop breast carcinoma.

In our series the results of radical mastectomy in the different age-groups were as shown in Tables I and II.

These data leave no doubt that radical mastectomy is worth while, even in the youngest patients with breast carcinoma, provided, of course, that the lesion itself is not too far advanced. If the three patients under the age of 30 in our series whose tumor developed during pregnancy or lactation are excluded, as indeed they should be for reasons which we shall shortly demonstrate, the five-year cure rate in the remaining 15 young

CARCINOMA OF THE BREAST

TABLE I

RESULTS OF RADICAL MASTECTOMY ACCORDING TO QUINQUENNIAL AGE-GROUPS

Age-Group	No of Operations	Operative Deaths		5-Year Local Recurrence		5-Year Clinical Cures	
		No	Per Cent	No	Per Cent	No	Per Cent
Under 30	18	0		4	22 2%	4	22 2%
30-34	32	0		8	25 0%	10	31 3%
35-39	68	1	1 5%	23	33 8%	20	29 4%
40-44	121	3	2 5%	28	23 1%	46	38 0%
45-49	121	3	2 5%	28	23 1%	46	38 0%
50-54	100	3	3 0%	21	21 0%	15	43 0%
55-59	68	5	7 4%	17	25 0%	19	27 9%
60-64	58	1	1 7%	12	20 7%	17	29 3%
65-69	35	2	5 7%	3	8 6%	17	48 6%
70+	19	2	10 5%	2	10 5%	9	47 4%
Total	640	20	3 1%	146	22 8%	231	36 1%

TABLE II

RESULTS OF RADICAL MASTECTOMY IN 18 WOMEN UNDER 30 YEARS OF AGE

Record No	Age	Origin During Preg or Lact	Metastases	5-Year Local Recurrence	Outcome
433589	22	No	0	0	Well five years
67803	23	Pregnancy	+	0	Died 4 months
56898	24	No	0	+	Died 25 months
409907	25	No	+	0	Died 39 months
224439	26	Lactation	+	+	Died 9 months
42141	27	No	Not proved	Not known	Living, with metastasis 9 years
361504	28	No	0	0	Died 27 months
15883	28	No	+	0	Died 59 months
34743	28	No	+	0	Died 29 months
384644	29	No	+	0	Died 9 months
408290	29	No	0	+	Recurrence 59 months Died 83 months
378962	29	No	+	0	Well 6 years
347901	29	No	+	0	Died 52 months
288630	29	No	+	0	Died 22 months
257685	29	Lactation	+	0	Metastasis sacrum 59 months Died 111 months
230452	29	No	+	0	Well until local recur and met 8 yrs Died 10 yrs
67958	29	No	0	0	Well 10 years
50052	29	No	+	+	Died 18 months

patients rises to 37.5 per cent a figure quite comparable with the cure rate for our series of cases as a whole.

Indeed, when the patients in our series are grouped according to age into broader categories there is surprisingly little difference in the results of operation in the different groups. Table III brings this fact out.

TABLE III

RESULTS OF RADICAL MASTECTOMY IN THREE AGE-GROUPS

Age-Group	No of Operations	Operative Deaths		5-Year Local Recurrence		5-Year Clinical Cures	
		No	Per Cent	No	Per Cent	No	Per Cent
Under 45	239	4	1 7%	63	26 4%	80	33 5%
45-59	289	11	3 8%	66	22 8%	108	37 4%
50 or over	112	5	4 5%	17	15 2%	43	38 4%
Total	640	20	3 1%	146	22 8%	231	36 1%

The surgeon dealing with breast carcinoma is also interested in the problem presented by patients of advanced age. Armed, as we are today, with methods of preventing and combating shock, we can perform, successfully, extensive surgical procedures upon aged patients upon whom we would not have dared operate previously.

In the present series there were a total of 45 women, age 70, or over, among the 876 primary cases. In 15 of these the carcinoma had progressed beyond the operable stage when they were first seen, while 12 were classed as constitutionally inoperable because of cardiovascular or other associated lesions (seven of these patients not only had inoperable cancer but were also judged constitutionally inoperable). Only four patients, ages 71, 74, 75, and 83, respectively, were denied radical mastectomy on the basis of advanced age alone. Twenty-one were judged suitable for the operation, but two of these refused it. Among the 19 who underwent it the results were surprisingly good. Nine or almost one-half, were alive and well at the end of five years, and the average length of survival of those who have had no recurrence of their carcinoma has, to date, averaged 87 months. The most noteworthy case is that of a woman who had her radical operation at the age of 78, and today, at the age of 89 is still hale and hearty.

We are led by this evidence to conclude that radical mastectomy is often feasible and worth while in patients in their eighth decade who come with breast carcinoma. Patients in their eighties present a more difficult problem. Even when their general condition is good we have hesitated to perform radical mastectomy. Perhaps we are too cautious. As our experience with surgery on patients in their eighties increases we may learn that radical mastectomy is reasonably safe even in this group. During the past year, however, we have instead, chosen to carry out simple mastectomy under regional block anesthesia on two patients age 89. In the series of 640 radical mastectomies, which are the subject of the present report, there were none undertaken upon patients in their ninth decade.

In operating upon these elderly patients it is much more important to *avoid* shock than to treat it well after it has developed. Shock has a much higher mortality in them than in younger patients. It becomes, so to speak, irreversible, and death follows from cerebral hemorrhage or cardiac failure.

The degree of decrepitude which the patient shows, and particularly the condition of her cardiovascular system, are, of course, more important than her age in itself in judging her ability to withstand radical mastectomy. While we have repeatedly performed the operation upon patients in their seventies, whose general condition was good, we have decided against attempting it upon some women in their sixties with severe hypertension, for instance. Among the total of 236 primary cases in which radical mastectomy was not performed in the present series there were 24 in which the basis for withholding the operation was the presence of some disease other than carcinoma. All of these had cardiovascular lesions of some type. One patient, in addition, had severe colitis, another diabetes and a third hyperthyroidism.

Certainly these two latter diseases do not, today, in themselves, contraindicate radical mastectomy. We have performed it in a number of patients after these disturbances have been brought under control by appropriate treatment.

Cardiovascular lesions present a more difficult problem. We have placed a good deal of reliance upon the simple functional test of stair-climbing. If a patient has been able to carry on a certain amount of daily physical activity which includes climbing even a single flight of stairs without acute distress we have judged her able to withstand radical mastectomy. In patients with hypertension we attempt to choose an anesthetic that neither depresses nor elevates the blood pressure unduly. Dr. Apgar, Director of the Department of Anesthesia in the Presbyterian Hospital, prefers nitrous oxide anesthesia for such patients, and warns against the use of avertin as a basic anesthesia for them because of its well known tendency to depress the blood pressure. In passing, it might be noted that avertin-nitrous oxide anesthesia is our favorite for these long breast dissections, provided there is no special contraindication to it.

PREGNANCY AND LACTATION

In view of the great stimulus to growth that the breast receives with the onset of pregnancy, and its active metabolism during lactation, it is but natural that a carcinoma developing during this period should be exceptionally malignant. This has, indeed, been the experience of all surgeons who have faced the problem. Yet there is a diversity of opinion as to the degree to which the malignancy of breast carcinoma is increased by pregnancy and lactation, and a corresponding lack of agreement as to whether or not pregnancy should be interrupted, and whether radical mastectomy should or should not be performed. In recent years data regarding this question have been presented by Bromeis,³ from the University Surgical Clinic, at Tubingen, and by Harrington,⁴ from the Mayo Clinic. Neither of these authors, however, tell us how many lasting cures were achieved in their clinics—they write only of survivals.

In the Presbyterian Hospital series of 876 primary cases there were 29 in which the breast carcinoma developed during pregnancy or lactation. In 20 of these women radical mastectomy was carried out (Table IV). There were no permanent cures. One patient remained well until six years after operation, when she developed local recurrence and pulmonary metastases, and died after another 18 months.

The results look better when expressed in terms of five-year survival, as Harrington presented them. Three, or 15 per cent of our 20 patients, were alive five years after operation, although all three succumbed later. Harrington reported the results of operation in a total of 99 women in whom breast carcinoma occurred during pregnancy or lactation. Thirteen of them, or 13.2 per cent, survived for at least five years. Thirty-two of his patients were traced 20 years after operation, and only one was found to have survived.

Another way of estimating the comparative malignancy of carcinoma of

the breast developing during pregnancy or lactation is in terms of the frequency of axillary metastasis. In our series of 20 cases that were operated upon 19, or 95 per cent were found to have axillary involvement. The incidence of axillary involvement in our total series of 640 breast carcinoma was on the other hand 61.7 per cent. In Harrington's series of 99 cases of breast carcinoma developing during pregnancy or lactation the axillary nodes were found to be involved in 84.8 per cent as compared with an incidence of 61.6 per cent in his series as a whole.

TABLE IV
CARCINOMA OF THE BREAST DEVELOPING DURING PREGNANCY OR LACTATION
AND TREATED BY RADICAL MASTECTOMY

Case No.	Age	Time of Appearance	Axillary Metastases	5 Year Local Recurrence	Site of Metastases	Follow up
20616	37	6 mos. preg.	+	+	Other breast	Died 13 mos. postop
27799	43	16 mos. before preg.	+	+	Bones	Died 25 mos. postop
59522	31	3 mos. lact.	0	+	Lungs	Died 41 mos. postop
67256	33	15 mos. lact.	+	0	None	Died lead therapy 5 mos. postop
67379	32	9 mos. lact.	+	0	Lungs and bones	Died 15 mos. postop
67803	23	Beginning of preg.	+	0	Other breast and bone	Died 4 mos. postop
71423	33	1 mo. preg.	+	0	Lungs	Died 8 mos. postop
80985	32	4 mos. preg.	+	0	Bones	Died 26 mo. postop
81542	36	16 mos. lact.	+	0	Liver	Died 5 mos. postop
224439	26	5 mos. lact.	+	+	Lungs and bones	Died 9 mos. postop
258421	34	30 mos. lact.	+	0	Bones	Died 11 mos. postop
350471	36	2 mos. before preg.	+	+	Bones	Died 17 mos. postop
375570	37	10 mos. before preg.	+	0	Lungs	Died 19 mos. postop
407734	38	48 mos. lact.	+	+	Other breast and lungs	Died 8 mos. postop
415597	12	6 mos. lact.	+	0	Bones	Died 43 mos. postop
64106	38	1 mo. before preg.	+	0	Lungs	Local recur. and met. 6 yrs. postop. Died 7½ yrs. postop
257685	29	16 mos. lact.	+	0	Bones and ovaries	Recur. 59 mos. postop. Died 111 months postop
57379	31	7 mos. lact.	+	0	Supraclav. node	Died 12 mos. postop
73673	44	7 mos. preg.	+	0	Lung	Recurrence 50 mos. postop. Died 66 mos. postop
232863	40	7 mos. lact.	+	0	Lungs, bones and liver	Died 33 mos. postop

These several types of evidence suggest to us that carcinoma of the breast developing during pregnancy or lactation is so malignant that surgery can not cure it often enough to justify this method of treatment. We prefer to classify these patients as *categorically inoperable* and to treat them palliatively with radiation.

When pregnancy occurs following the successful removal of carcinoma of the breast it has no special unfavorable prognostic significance. If the carcinoma has been entirely removed the growth stimulus of pregnancy has no effect. If, on the other hand, a focus of carcinoma cells persists somewhere in the patient's body their resurgence may of course be hastened by a subsequent pregnancy, but the patient would have been doomed eventually anyway.

so that the ultimate cure rate remains unaltered by the incident of pregnancy. Seven of our 640 patients treated by radical mastectomy subsequently went through one or more pregnancies. In this small group of seven the five-year cure rate was 42.9 per cent, approximately the same as in our patients who did not subsequently become pregnant. Harrington's experience was similar. Subsequent pregnancy occurred in 59 of his patients, and five-year survival rate was 78.2 per cent in the group.

Influenced by these facts it has been our custom not to deny pregnancy to patients who have satisfactorily gone through radical mastectomy and appear to have a favorable prognosis, i.e., no axillary metastases or other unfavorable features.

PHYSICAL SIGNS OF EXTENT OF DISEASE WHICH EFFECT OPERABILITY

Not all of the many physical signs which breast carcinoma produces have a bearing upon operability. Thus, dimpling of the skin, deviation and retraction of the nipple, and distortion of the outline of the areola, which are among the most common signs of the disease, are important in diagnosis but, in themselves, they have no bearing upon the question of operability, which we are here discussing, for the patients with them are always operable unless some other physical sign makes it necessary to class them as inoperable.

But the significance of certain other physical findings in breast carcinoma such as ulceration and edema, is not generally agreed upon. There has been a dearth of satisfactory and detailed data regarding them. It is to these physical signs of problematic prognostic significance that we will devote our attention.

THE SITE OF CARCINOMA IN THE BREAST

The site of the tumor in the breast is one of these factors which comes first to mind. The relationship of the site of the tumor to the results of radical mastectomy in our series of cases is shown in Table V.

TABLE V
RESULTS OF RADICAL MASTECTOMY
ACCORDING TO THE SITE OF THE CARCINOMA IN THE BREAST

Site in Breast	No of Operations	5-Year Local Recurrence		5-Year Clinical Cures	
		No	Per Cent	No	Per Cent
Upper outer quadrant	277	51	18.4%	118	42.6%
Upper inner quadrant	78	17	21.8%	27	34.6%
Center	74	22	29.7%	24	32.4%
Lower outer quadrant	51	8	15.7%	17	33.3%
Lower inner quadrant	28	11	39.3%	6	21.4%
Upper half	47	10	21.3%	14	29.8%
Lower half	15	3	20.0%	5	33.3%
Outer half	35	15	42.9%	7	20.0%
Inner half	5	3	60.0%	2	40.0%
Entire breast	15	5	33.3%	2	13.3%
Not stated	15	1	6.7%	9	60.0%
Total	640	146	22.8%	231	36.1%

These data confirm the general experience that the upper outer sector of the breast is the one most frequently affected by the disease. Moreover, the best results of operation are obtained with tumors in this same sector. Perhaps this is because surgeons who perform the standard radical operation, and close their wounds, are able to remove the tumor with a wider margin of uninvolved surrounding tissues when it is situated in the upper outer sector than when it is in any other part of the breast.

There is one situation in which breast carcinoma occasionally develops which is not listed in our table, namely, the inframammary region. We are today familiar with this form of breast carcinoma, but it was not identified as a special type of the disease by most of the surgeons who, in years gone by, wrote the descriptions of the cases here reported. We are unable, therefore, to present data regarding it.

It is our impression, however, from the patients with carcinoma in the inframammary fold which we have personally observed, that this form of the disease is a particularly favorable one. Patients are apt to detect a tumor in this situation early, because it is not hidden in the depths of surrounding fatty breast tissue but stands out in sharp relief along the fold where the fascia covering the breast fuses with the fascia covering the abdominal wall.

From the standpoint of operability, there is no site in the breast in which carcinoma can be deemed beyond the scope of surgical attack. When the entire breast is involved the results are poor, but this question of the significance of the extent of the local disease is better discussed on the basis of actual measurements of the tumor. It is the next factor which we shall discuss.

THE SIZE OF THE BREAST TUMOR

The importance of making careful measurements, preferably in centimeters, of all breast tumors can not be too strongly emphasized. Fortunately, such measurements were available in the great majority of our cases. The correlation between results of radical mastectomy and the size of the tumor in our series is shown in Table VI.

TABLE VI
RESULTS OF RADICAL MASTECTOMY ACCORDING TO THE SIZE OF THE BREAST TUMOR
(Clinical Measurements)

Size of Tumor	No. of Operations	5 Year Local Recurrence		5 Year Clinical Cures	
		No	Per Cent	No	Per Cent
Under 30 mm	82	11	13.4%	51	62.2%
30 to 59 mm	256	50	19.5%	110	43.0%
60 mm. or over	222	74	33.3%	43	19.4%
Size not stated	80	11	13.8%	27	33.8%
Total	640	146	22.8%	231	36.1%

These data indicate, as might be expected, that the prognosis becomes worse as the size of the tumor increases. Local recurrence is more frequent and the five-year clinical cure rate is lower.

But large size, alone, is no contraindication to operation. Even the largest breast carcinomata, if they do not exhibit any unfavorable feature other than their large size, can often be cured by surgery. Table VII illustrates this point. In it are shown the results of operation in 19 cases in which the primary tumor in the breast measured ten centimeters, or more, in diameter. Cases which we have classified as *categorically inoperable* for several reasons, and which we will discuss in detail later on in this report, have not been included in this table.

TABLE VII

RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THE TUMOR MEASURED TEN CENTIMETERS, OR MORE, IN DIAMETER
(Clinical Measurements)
(Categorically Inoperable Cases Excluded)

Physical Findings	No of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No	Per Cent	No	Per Cent
10 cm., or more, tumor <i>only</i>	12	2	16.7%	3	25.0%
10 cm., or more, tumor <i>with</i> * signs of locally advanced disease	7	2	28.6%	1	14.3%
Total	19	4	21.1%	4	21.1%

The size of the breast tumor bears a general relationship to its duration, or rather to the duration which the patient alleges. This relationship is shown in Table VIII. In this table the measurements used are those made by the pathologist after the specimen has been cut. It is noteworthy that some tumors remain small even after they have been present for a long time.

TABLE VIII

RELATIONSHIP OF THE SIZE OF THE TUMOR (PATHOLOGIC MEASUREMENTS) TO ITS DURATION

Size of Tumor	No of Operations	Duration				Not Stated
		Under 1 Mo	1 to 5 Mos	6 to 11 Mos	1 Yr +	
Under 20 mm	64	18	26	9	9	2
20-49 mm	272	46	98	43	60	25
50 mm +	182	17	68	43	46	8
Not stated	122	19	44	24	25	10
Total	640	100	236	119	140	45

Although the probability of finding axillary metastases increases as the breast tumor enlarges, it is distressing to note that even in the group of

* In this, and in the following tables dealing with the prognostic significance of other individual features of breast carcinoma, the signs of locally advanced disease referred to are the ones which we have found from our data to have the gravest prognostic import. They include ulceration of the skin, edema of the skin, fixation of the breast tumor to the chest wall, axillary lymph nodes measuring 2.5 cm., or more, in transverse diameter, and fixation of the axillary nodes to the chest wall or overlying skin.

cases with the smallest tumors (under 20 mm in diameter) the incidence of axillary metastasis is large, to be exact 43.8 per cent. These data are shown in Table IX. Again the measurements used are those made by the pathologist.

TABLE IX

RELATIONSHIP OF THE SIZE OF THE TUMOR (PATHOLOGIC MEASUREMENTS) TO AXILLARY METASTASIS

Size of Tumor	No. of Operations	Axillary Metastasis		Axillary Nodes Not Examined
		No.	Per Cent	
Under 20 mm	64	28	43.8%	0
20-49 mm	272	151	55.5%	7
50 mm +	182	135	74.2%	3
Not stated	122	71	58.2%	8
Total	640	385	60.2%	18

MULTIPLE TUMORS IN ONE BREAST

Pathologic study not infrequently reveals that breast carcinoma exists in multiple foci in the affected breast, particularly in the relatively advanced cases, but these multiple tumors are not often detected clinically. We do not refer of course to satellite tumor nodules in the skin but to separate foci of carcinoma within the breast tissue itself. In our series there were only twelve such cases diagnosed clinically among the 640 in which radical operation was performed. It is probable that more careful palpation would reveal them more often.

Although our group of cases is small after the *categorically inoperable* ones have been excluded, Table X shows that the results of operation were relatively good in the 12 cases in which the multiple nature of the disease in the affected breast was the only prognostic factor that had to be considered. In the three cases in which there were multiple tumors and in addition, other signs of locally advanced disease there were, however, no cures.

TABLE X

RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THERE WERE MULTIPLE TUMORS IN ONE BREAST
(Clinical Diagnosis)
(*Categorically Inoperable Cases Excluded*)

Physical Findings	No. of Cases	5 Year Local Recurrence		5 Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Multiple tumors only	9	3	33.3%	4	44.4%
Multiple tumors with signs of locally advanced disease	3	1	33.3%	0	—
Total	12	4	33.3%	4	33.3%

LOCAL ELEVATION OF SKIN TEMPERATURE

Our personal study of breast tumors has convinced us that careful comparison of the skin temperature over the tumor with that of a corresponding

skin area on the opposite breast will often show that the skin over the tumor is warmer. Although this sign is most frequently found in carcinoma we have observed it in a variety of types of benign tumors and we do not attach any special diagnostic significance to it.

We are unable to present any data regarding the prognostic significance of elevation of skin temperature because most of the surgeons who, in years gone by, wrote the descriptions of the cases reported in this series did not make any note of this sign.

REDNESS OF THE SKIN

Redness of the skin is sometimes a striking feature of breast carcinoma. While in the far-advanced cases it is seen as the result of actual involvement of the skin by the disease, in earlier ones it may develop merely as part of an inflammatory-like reaction which some carcinomata induce in the tissues which surround them.

TABLE XI
RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THERE WAS REDNESS OF THE SKIN
(Categorically Inoperable Cases Excluded)

Clinical Group	No. of Cases	5-Year Local Recurrence		5 Year Clinical Cures	
		No.	Per Cent	No.	Per Cent
Redness only	23	6	26.1%	8	34.8%
Redness with signs of locally advanced disease	30	13	43.3%	6	20.7%
Total	53	19	35.8%	14	26.4%

Table XI shows the results of radical mastectomy in the cases in the present series in which redness was noted, excluding the ones classified by us as *categorically inoperable*. Among these latter is the group of so-called "inflammatory" carcinomata in which redness is a prominent feature of the clinical syndrome. It will be seen from this table that redness occurring alone does not imply a bad prognosis. When it occurs with other signs of locally advanced disease, however, the outlook is considerably poorer.

INVOLVEMENT OF THE SKIN

Involvement of the skin over the tumor, as we have used it in the present classification, refers to those cases in which the skin over the tumor has become fixed and immovable. This is a clinical and not a pathologic criterion. It does not include the cases in which this involvement has progressed to the point of ulceration, these form a separate group which we shall discuss subsequently.

Table XII shows the results of radical mastectomy in these cases with skin involvement, excluding the ones classified by us as *categorically inoperable*. From this table it would appear that skin involvement occurring alone

TABLE XII
RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THERE WAS INVOLVEMENT OF THE SKIN
(Categorically Inoperable Cases Excluded)

Clinical Group	No of Cases	5 Year Local Recurrence		5 Year Clinical Cures	
		No	Per Cent	No	Per Cent
Skin involvement <i>only</i>	21	6	28.6%	6	28.6%
Skin involvement <i>with</i> signs of locally advanced disease	44	11	25.0%	8	18.2%
Total	65	17	26.2%	14	21.5%

does not imply a bad prognosis, although when it occurs with other signs of locally advanced carcinoma the percentage of cures decreases

ULCERATION OF THE SKIN

Ulceration of the skin over a breast tumor is a sign that surgeons know well, and most of them have learned that it does not necessarily mean that the case is hopeless

TABLE XIII
RESULTS OF RADICAL MASTECTOMY
CASES IN WHICH THERE WAS ULCERATION OF THE SKIN
(Categorically Inoperable Cases Excluded)

Clinical Group	No of Cases	5-Year Local Recurrence		5-Year Clinical Cures	
		No	Per Cent	No	Per Cent
Ulceration <i>only</i>	9	1	11.1%	2	22.2%
Ulceration, <i>with</i> other signs of locally advanced disease	14	4	28.6%	1	7.1%
Total	23	5	21.7%	3	13.0%

Our data, as shown in Table XIII, bear out the truth that ulceration of the skin *occurring alone* does not indicate an unusually bad prognosis. When it occurs together with other signs of locally advanced disease, however, the outlook is indeed poor, in our series the cure rate for such cases was only 7.1 per cent. It should be noted that the cases classified by us as *categorically inoperable* have been excluded from this table

(To be continued)

IMMEDIATE EFFECTS ON RENAL FUNCTION OF THE ONSET OF SHOCK DUE TO PARTIALLY OCCLUDING LIMB TOURNIQUETS*

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IN A REVIEW of the status of the shock problem, Wiggers (1942) has referred to the lack of quantitative knowledge which would point to the presence of vasoconstriction sufficient to increase greatly resistance in important visceral vascular beds or, by its intensity and persistence, great enough to lead to capillary damage. Clinical observations testify to a slowing of peripheral blood flow and contraction of cutaneous vessels during the early stages of shock and quantitative measurements have confirmed this (Freeman, Shaw and Snyder, 1936, and Baldes, Herrick, Essex and Mann, 1941). Precise information as to visceral vascular changes was largely lacking until Page and Abell (1943) directly observed mesenteric arteriolar vasoconstriction during the onset of shock. The demonstration of a concurrent and intense renal vasoconstriction would signify an increase in vascular resistance in another and a very large set of vessels since the kidney normally receives some 20 per cent of the cardiac output in the dog (Mason, Blalock and Harrison, 1938, and Levy and Blalock, 1937), and rather more in man (Smith, 1939). Fortunately this demonstration may be quantitatively made by applying the methods and principles of Van Slyke, Rhoads, Hiller and Alving (1934), and of Smith, Goldring and Chasis (1939). The deficit in information to which Wiggers referred may thus be overcome.

Changes of renal blood flow and function during shock are of current interest also, since they may in a measure explain the pathogenesis of renal failure in "traumatic anuria" ("crush syndrome"). It was with reference particularly to this problem that the work here reported was begun. Briefly, the present report consists of a description of the variations of renal hemodynamics and function which may occur during the onset of shock in anesthetized dogs after renal denervation, and after splenectomy, and during the transfusion of blood. The choice of partially occluding limb tourniquets as a method of producing shock was made because of its simulation of the conditions under which clinical traumatic anuria may occur, and because, in contrast to many procedures, it permits continuous observation of systemic changes.

METHODS

Our observations were made during 14 experiments upon dogs anesthe-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Lilly Laboratory for Clinical Research.

tized with sodium pentobarbital (Lilly) given in a dose of 30 mg per kilo of body weight¹. In some experiments small additional doses of anesthetic were given to maintain an even depth of anesthesia. Two experiments were undertaken in otherwise normal uninephrectomized dogs with one subcutaneously explanted kidney (method of Page and Corcoran 1940), both operations having been performed three years before. Blood was transfused in one of these, and acacia solution given the other. Two experiments were made in a normal dog not treated by transfusion and two in two normal dogs treated by transfusion. Blood was also given during an experiment upon a dog suffering from renal hypertension (method of Page 1939). Observations were made in one dog whose legs were firmly wrapped in plaster encasements. Six experiments were done in dogs both of whose kidneys had been denervated 10 to 14 days before the experiment. Splenectomy had been performed in five of these at the time of renal denervation and these five dogs were given blood during the experiment while the non-splenectomized subject was treated by infusion of acacia. The grouping of the experiments is shown in Table I.

3

TABLE I

Type of Experiment	No. of Experiments
A Normal dogs	
(a) Nontransfused one with renal infused	1 2 3
(b) Transfused	4 5, 6
B Dogs with denervated kidneys	
(a) Splenectomized blood transfused	7 8 9 10
(b) Nonsplenectomized renal infused	11
C Other experiments	
(a) Renal hypertension	12
(b) Legs wrapped in plaster encasements	13
(c) Collapse not relieved by transfusion	14

In outline each experiment consisted of (1) a control period of some 30 minutes of observation, following which (2) partially occluding limb tourniquets were applied. The observations were continued for about four hours when (3) the tourniquets were removed and the experiment continued for another 80 minutes or more. Some of the animals were sacrificed and examined at the end of this time, but the majority died 8 to 14 hours after the application of the tourniquets. One animal was allowed to recover and the experiment repeated. The blood which was given was cross-matched and freshly drawn from a donor into a vacuum flask containing sodium citrate solution. It was given to the recipient by intravenous infusion started before the release of tourniquets. The tourniquets consisted of stout cord and were so applied at the junction of thigh and body that a slow arterial inflow persisted for a time. The legs swelled for an hour or more after

¹ A study now in press (Corcoran and Page, Amer. J. Physiol. 1943) establishes that anesthesia was not the cause of the effects here reported except possibly in Experiment 14.

their application, when swelling ceased, to begin again after the cords were released by cutting them free. Blood pressure was measured by a mercury manometer connected to the cannulated carotid artery. The arterial pressure usually rose immediately after application of the tourniquets and fell slowly although not to "shock levels" while they were in place. Blood pressure fell abruptly when the cords were cut, but soon returned to nearly the previous level. Following this, the pressure fell slowly to hypotensive levels during the ensuing hours. The aim of blood transfusion in these experiments was to maintain arterial pressure at approximately normal levels, blood was, therefore, given slowly while the tourniquets were in place, rapidly immediately after their release, and then again more slowly. The course of the shock which follows this procedure in dogs is described in detail by Taylor and Page (1943).

The observations made during the experiments include the renal clearances of diodrast and inulin, urine volume, arterial pressure and hematocrit index (method of Wintrobe). The proportions of diodrast and inulin removed by the kidneys were observed by sampling renal venous blood in the dogs with subcutaneously explanted kidneys. From these proportions (renal extraction ratios) and the plasma clearances, total renal blood and plasma flows were calculated. The levels of total plasma protein were measured in an experiment upon a normal dog. Page (1943) had demonstrated during shock the development of a substance in plasma which constricts the isolated perfused vessels of a rabbit's ear which, pending identification, he has termed "peripheral vasoconstrictor substance." Measurements of this kind were made in seven of the experiments.

For the measurement of clearances, a solution containing diodrast and inulin and 2 per cent of sodium sulfate in physiologic saline solution was infused intravenously, and the rate of infusion varied to maintain the plasma concentrations of diodrast-iodine at 1 to 5 mg per 100 cc, and of inulin at 30 to 60 mg per 100 cc. A "priming" dose of the infusion fluid was given 30 minutes before the start of the experiment, and the infusion continued at a rate of 2 cc per minute or less. Diodrast-iodine was determined in plasma and urine by the method of Corcoran and Page (1943), which utilizes the colorimetry proposed by Flox, Pitesky and Alving (1942). Inulin determinations were done by the method of Corcoran and Page (1939). A soft rubber retention catheter was inserted and the urine collected by careful bladder washing and compression. Urine volume was calculated from the excess volume of urine \pm washing fluid. This method of estimating urine volume is, of course, not precise at low levels of urine flow and over short period of collection although it suffices to demonstrate large changes. However, during the experiments, the periods of collections were prolonged during oliguria, so that the measurements may be accepted as approximating closely the rate of urine secretion. The determination of plasma protein content was made by an adaptation of the method of Kingsley (1942) to the Evelyn photo-electric colorimeter.

RESULTS

A Normal Dogs—(a) *Nontransfused* 1. Effects of Tourniquet Application. The courses of these experiments (Nos. 1, 2 and 3) are summarized in Chart 1, in which the variations observed are averaged as percentage of change from the control levels. The mean duration of tourniquet application was 215 minutes. During^a the first 15 minutes the plasma clearances de

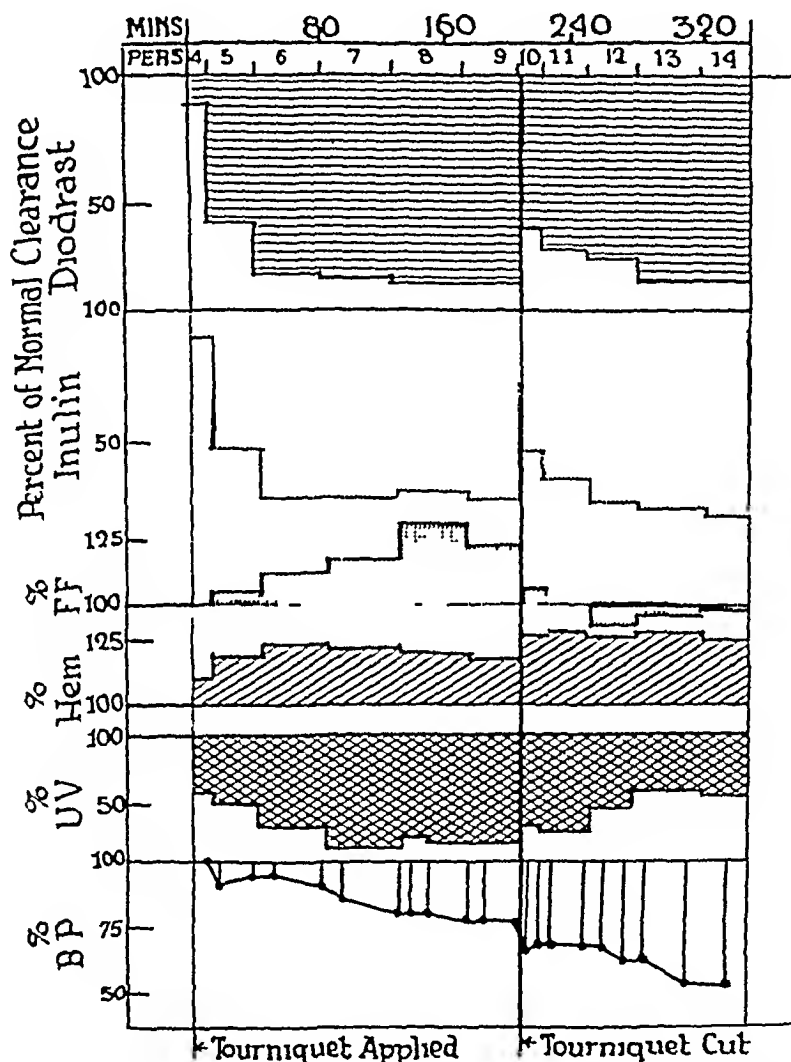


CHART 1—Means of percentile variations from control levels of diodrast clearance, inulin clearance, filtration fraction (F F), hematocrit index (Hem), urine volume, (U V) and blood pressure (B P) induced by application and release of partially occluding limb tourniquets in three normal dogs. Abscissa: mins = minutes from application of tourniquets, pers = periods of urine collection.

creased by 12 per cent, decreases to about 45 per cent occurred during the next 30 minutes and were followed by further decreases to approximately 25 per cent, at which levels they were maintained. Filtration fraction rose to range between 112 and 131 per cent of the control after the first 15 minutes because of a greater depression of diodrast than inulin clearance. Urine volume was depressed to from 13 to 28 per cent of the control level. Arterial pressure was not altered at first, but after 15 minutes fell slowly

to reach 75 per cent of the control level at the time the tourniquets were released. Hematocrit index increased immediately after application of the tourniquets by 8 per cent, and reached 122 per cent of the control after 45 minutes. The blood loss from sampling in Experiments 1 and 2 was about 60 cc, including that taken during control periods.

The observations in Experiment 3, upon a dog with a single subcutaneously explanted kidney are of especial interest since they provide means of assessing the significance of the clearance changes observed in nonexplanted dogs. Briefly, application of tourniquets did not significantly alter diodrast extraction ratio, which was depressed by only 5 per cent during the whole time, on the other hand, the extraction ratio of inulin was doubled. The fact that diodrast extraction ratio was maintained near control level (0.77) while plasma diodrast clearance fell to about 20 per cent of the control level, indicated that the change in clearance was the result of decreased renal blood flow. Inulin clearance was not as severely depressed because the inulin extraction ratio rose in proportion to the filtration fraction. Plasma total protein decreased from 5.8 to 5.3 Gm per 100 cc during the tourniquet application. Total blood loss due to sampling during this time was 190 cc. In spite of this loss, hematocrit index increased from 41 to 47 per cent.

2. **Tourniquet Release.** Release of the tourniquets caused a sharp fall in arterial pressure for about one minute, after which pressure was restored but at a lower level than before. In two of the three experiments the plasma clearances of diodrast and inulin nevertheless increased. Filtration fraction fell in all three. Urine volume remained low. Hematocrit index was increased. Release of the tourniquets was followed by a slight initial fall in clearances in Experiment 3, which was maintained for about 15 minutes after the cords were cut, when these values fell precipitously. These changes in the clearances were associated with marked changes in diodrast extraction ratio which, in the four periods of observation, yielded values successively of 0.72, 0.68, 0.69, and 0.50. Inulin extraction was maintained at the high level reached during the presence of tourniquets until the last of these periods, when it was observed at zero as the arterial pressure fell to 60 mm Hg.

The duration of tourniquet application was 191 minutes in Experiment 1, and the dog recovered after the experiment. Experiment 2 was undertaken upon this dog nine days later, and the tourniquets applied for 210 minutes. Death ensued eight hours after beginning the experiment. Duration of application was 245 minutes in Experiment 3, and death occurred 11 hours after beginning the experiment. That renal function was not long affected by the severe changes which developed during Experiment 1 is shown in the clearances of diodrast and inulin were, respectively, 170 and 53 cc per minute in the control periods of Experiment 1 and 163 and 54 cc per minute at the start of Experiment 2.

Normal Dogs—(b) **Transfused.** 1. **Effects of Tourniquet Application.** The observations made in this group of three dogs are summarized in Chart

2. Blood was given intravenously starting about 90 minutes after tourniquet application, so that arterial pressure fell by only about 12 per cent. In spite of this partial maintenance of blood pressure, the clearances of diodrast and inulin fell in the manner observed in the first group, and so remained during the first 50 minutes of transfusion, after which the clearances rose to about 50 per cent of normal. Whereas the decrease of clearances had been associated with increased filtration fraction and oliguria the subsequent

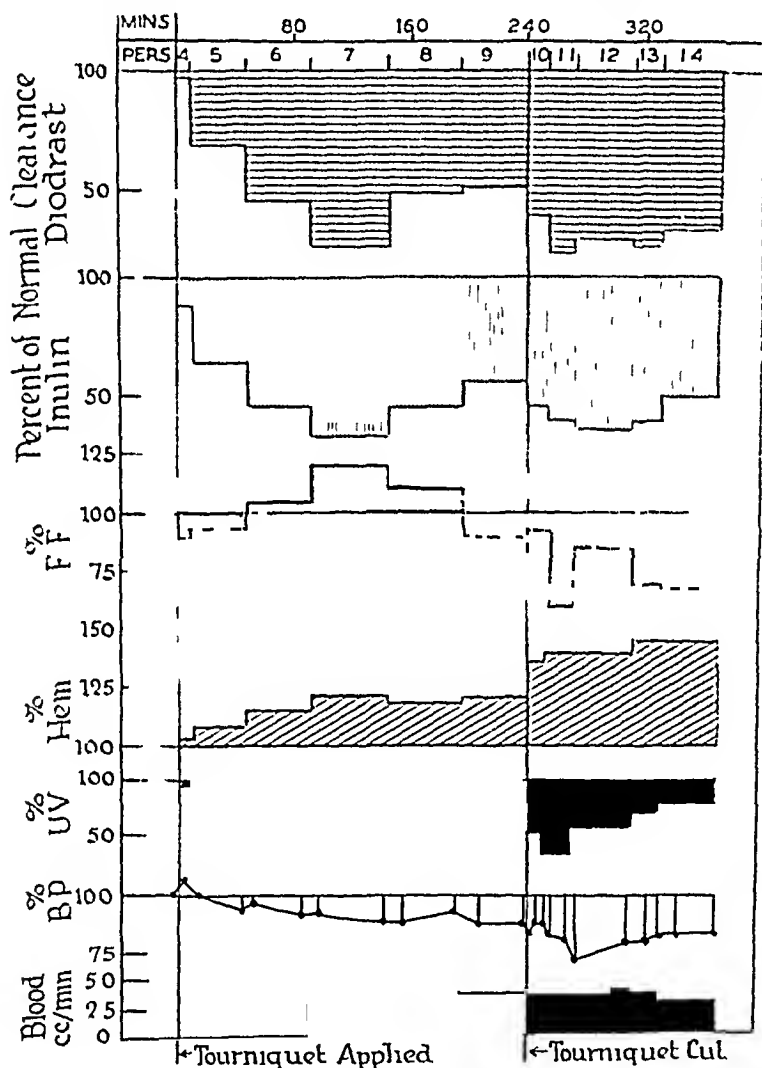


CHART 2—Legend as in Chart 1. The observations were made in three normal dogs transfused with blood during tourniquet application and release. Duration and rate of transfusion shown in blocked area at bottom, cc per min.

increase was accompanied by a fall in this value and an increase in urine flow. Hematocrit ratio, which had risen before transfusion, was maintained during it. "Peripheral vasoconstrictor substance" was measured in two dogs (Dogs 4 and 6) and shown to appear in the blood in increased amounts after application of tourniquets. The subject of Experiment 6 was one of the two dogs with subcutaneously explanted kidneys, as in the similar dog

(Dog 3) the presence of the tourniquets did not alter the renal extraction ratio of diodrast which was maintained at the control level of 0.68, during a fall of diodrast clearance to 30 per cent and a restoration by transfusion to 60 per cent of the control level. The levels of renal plasma flow, therefore, varied in parallel with those of plasma diodrast clearance. Unlike Experiment 3, the fall of clearance was not associated with a marked increase in inulin extraction ratio or in filtration fraction. This was because the greater decrease in systemic arterial pressure prevented the development of increase in intraglomerular pressure by efferent arteriolar constriction.

2 *Tourniquet Release* The transfusion of blood during and after the tourniquet release failed to prevent a fall in the clearances in the subsequent observations although it did maintain arterial pressure approximately at the level which was previously obtained. Filtration fraction and urine flow remained unchanged, the latter at about 50 per cent of the control level. The hematocrit index rose sharply to a maximum of 145 per cent of the control in the group. In Experiment 6 as in Experiment 3, diodrast extraction ratio fell after tourniquet release to successive levels of 0.55, 0.58, 0.58 and 0.65. Clearance and renal plasma flow were simultaneously depressed in spite of a well maintained arterial pressure. Inulin extraction ratios increased to levels ranging about 0.35 and, as a result the decrease of inulin clearance was less marked than that of diodrast and filtration fraction increased. "Peripheral vasoconstrictor substance" increased greatly in the blood of this dog just before transfusion and, although at a slightly lower level, remained increased during the experiment in which, in all, 700 cc of blood were given. One dog of this group (Dog 5) died 12 hours after the experiment, and the other two were sacrificed at its completion.

B *Renal Denervation*—(a) *Splenectomy Transfusion* 1 *Effects of Tourniquet Application* The results of four experiments are recorded together in Chart 3. As in the previous two groups, the clearances and the level of arterial pressure were not at first affected by application of tourniquets, but began to fall after about 15 minutes. But, in contrast, they fell only to levels of about 50 per cent of the control and no dog in the group showed the severe fall of clearance (to levels of 20 or 25 per cent of control) which characterized the nondenervated groups of dogs. Filtration fraction rose as the clearances began to decrease but was later restored to a normal level. Arterial pressure fell by about 18 per cent in spite of slow transfusion of blood as in the nondenervated transfused series (A—b). Urine volume was depressed roughly in proportion to clearance. Unlike the nonsplenectomized dogs, this group did not show an increase of hematocrit index.

2 *Tourniquet Release* The transfusion was speeded as the tourniquets were released and arterial pressure rapidly restored to the level (83 per cent of control) which presented before they were cut. Probably because of hypotension the clearances fell at first to about 20 per cent of the control and rose to 50 per cent being ultimately brought nearly to the control level. Hematocrit ratio now began to rise and the increase continued after the

transfusion was discontinued. Urine volume, which had fallen only slightly after release of the cords, rose to exceed the control level when pressure was restored towards the control level.

Two dogs in this group died at 10 and 12 hours after the start of the experiment, while two were sacrificed at its conclusion.

(b) Splenectomy Nontransfused Delayed Infusion of Acacia. Only one such experiment was satisfactorily completed. The presence of the

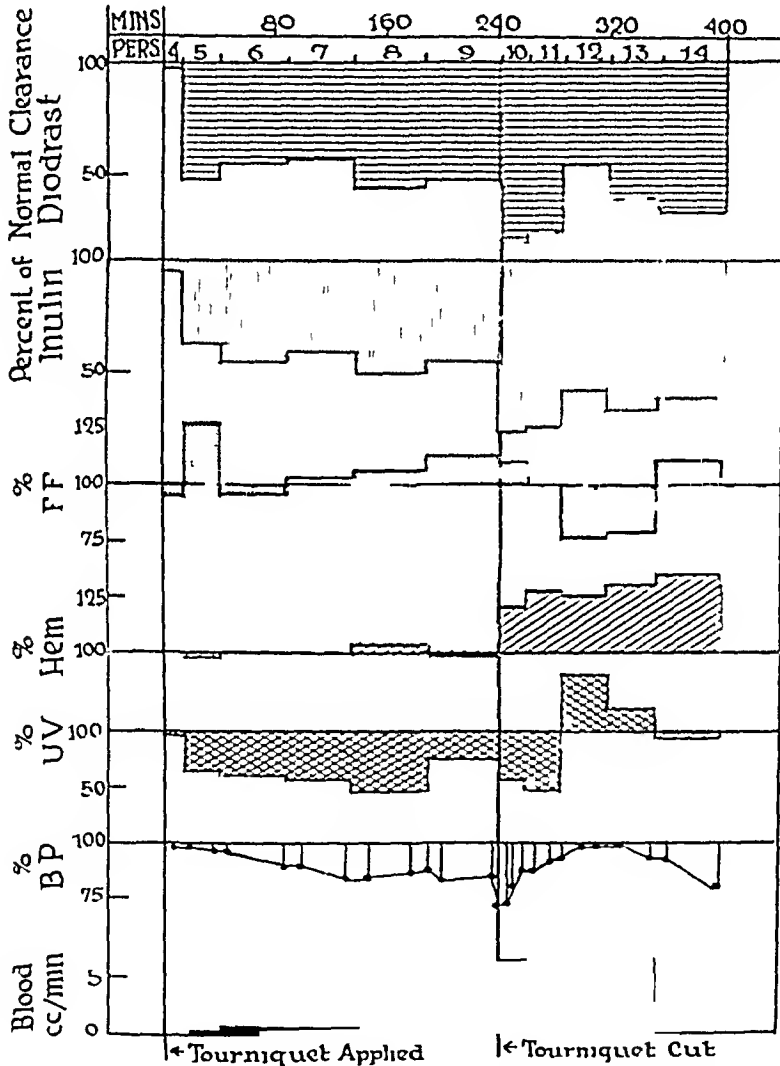


CHART 3—Legend as in Charts 1 and 2. Observations made in four dogs previously subjected to renal denervation and splenectomy.

tourniquets caused a fall in clearance levels only to about 70 per cent of the control. During this time filtration increased and urine flow was greatly depressed. Arterial pressure reached a minimum of 60 per cent of the control just before release of the tourniquets when they had been on for 250 minutes. The hematocrit index reached 134 per cent of the control immediately after application of the tourniquets and fell slowly afterwards. Re-

lease of the tourniquets caused a sharp fall in arterial pressure to 43 per cent of the control and a subsequent rapid rise to 50 per cent, i.e., 67 mm Hg. During this time the clearances fell to 13 and 1 per cent of the control levels, and urine flow almost ceased, while the hematocrit index rose sharply to 154 per cent of control. A 6 per cent solution of acacia was then given at a rate of nearly 20 cc per minute for 26 minutes and the arterial pressure brought to 90 per cent of normal. During this time the clearances rose rapidly, only to fall again with arterial pressure when the infusion was stopped. Hemoglobinuria developed during these observations, and death occurred ten hours after the start of the experiment.

C Other Experiments—(a) Renal Hypertension. One experiment was undertaken in a dog suffering for one year from mild hypertension due to bilateral perirenal application of silk (Page, 1939). As in normal dogs, the plasma clearances decreased after application of tourniquets to reach about 30 per cent of the control, when pressure had fallen, by 26 per cent, to 152 mm Hg. Transfusions of blood then rapidly restored the level of arterial pressure nearly to the control, although the plasma clearances remained depressed by about 20 per cent. The hematocrit index had meanwhile risen to about 150 per cent of the control, so that assuming that plasma diodrast clearance is equivalent to renal plasma flow, renal plasma flow was depressed while renal whole blood flow was actually increased. Release of the tourniquets did not further lower arterial pressure which increased to the control level as transfusion continued, as did the plasma clearances of diodrast and inulin. The hematocrit index remained high, so that apparent total renal blood flow further increased above the normal as was also urine flow. It is noteworthy that measurements of "peripheral vasoconstrictor substance" showed no development of this material in the blood during the experiment.

(b) Effect of Limb Encasements. Snugly fitting plaster encasements were applied to the legs of one dog from foot to thigh before the control periods. That such a procedure does not affect clearance is shown in the fact that the values obtained during the control periods of the experiment were identical with those previously observed in this dog when conscious. The course of this experiment is shown in Table II, from which it will be seen that application and release of the tourniquets under this condition did not alter renal function.

(c) In Experiment 14 upon an apparently normal dog, arterial pressure began to fall from the control of 133 mm Hg 40 minutes after application of tourniquets, and continued to fall in spite of rapid intravenous transfusion of blood, and was only temporarily stabilized at 100 mm Hg after the infusion of 600 cc of blood (roughly, 0.6 of this animal's probable blood volume). The fall in pressure was associated with a severe reduction of renal clearances, which were restored only to 50 per cent of the control when the pressure was brought to 100 mm Hg, while oliguria continued. After 92 minutes, the experiment was discontinued and the tourniquets released. The dog died 15 hours from the start of the experiment.

TABLE II

SEQUENCE OF OBSERVATIONS IN A DOG BOTH OF WHOSE KIDNEYS WERE SECURELY BOUND WITH PLASTER BANDAGES BEFORE STARTING THE EXPERIMENT. THE TIME OF EACH PERIOD OF URINE COLLECTION IS INDICATED IN MINUTES. THE ASTERISK OPPOSITE THE ARTERIAL PRESSURE (PERIOD 9) INDICATES THAT IT DROPPED MOMENTARILY TO 156 MM. HG. AS EACH TOURNIQUET WAS RELEASED.

Urine Collection Period	Plasma Clearances			Urine Vol. Ce. Per Min.	Hematocrit Index Per Cent	Arterial Pressure Mm. Hg.	Time Min.	Remark
	Diodrast Cc. Per Min.	Inulin Per Min.	Filtration Fraction					
1-3	248	81	0.32	0.2	56	158	50	Control
4	258	77.1	0.30	0.15	59	148	46.75	(2) Tourniquets
5	265	75.6	0.28	0.12	58	158	16.0	applied
6	236	69	0.29	0.11	56	158-166	18.25	
7	231	71.1	0.31	0.18	57	168	47.25	
8	234	72	0.30	0.3	57	166	17.0	
9	213	73.4	0.31	0.15	57	161*	12.25	(1) Tourniquets
10	216	82.5	0.31	0.2		166	20	released
11	223	73	0.33	0.1	57	166	21.5	

DISCUSSION

The death of many animals in this series indicates that the observations reported were in fact made during 'the onset of shock.' This view is supported by the clinical and anatomic evidences of death in shock which appeared in 15 normal and 12 splenectomized dogs subjected to a similar four-hour period of tourniquet application (Taylor and Page 1943). We are therefore, lead to believe (Chart 1) that the onset of shock due to tourniquet application and release is associated with severe depression of renal function.

The oliguria may result in a measure from secretion of hypophyseal antidiuretic hormone as the result of painful stimulation (Radin and Verney 1938) for it had its onset often before large changes in the renal clearances of diodrast and inulin. As to the latter the observations in the dogs with subcutaneously explanted kidneys establish that, as in normal dogs (White and Hembecker, 1940, and Corcoran, Smith and Page, 1941) plasma diodrast clearance during tourniquet application may be considered as measuring the rate of renal plasma flow to functioning excretory tissue (Smith, Goldring and Chasis 1938) while plasma inulin clearance is accepted as the measure of the rate at which glomerular filtrate is formed from renal plasma (Smith 1939). By this construction the depression of renal function which appears during the onset of shock is essentially due to reduction of renal blood flow. It, thus becomes our purpose to determine the nature and origin of this renal ischemia.

Renal ischemia during shock might be due to hypotension alone or to some redistribution of blood in response to decreased blood volume. Actually a comparison of the levels of renal perfusion and arterial pressure 45 minutes after tourniquet application with these values in hypotension due to a large hemorrhage (Corcoran and Page 1943) indicates that the reduction of blood flow is not simply the result of lowered arterial pressure and decreased blood volume. This impression is confirmed by the experiments summarized in Chart 2 where transfusion of large amounts of blood caused

only a modest restoration of renal plasma flow towards the normal. The renal ischemia of early shock is, therefore, not the result of hypotension and, it follows, that it must arise in increased renal resistance to the flow of blood. That renal resistance rises is shown graphically in Chart 4, where are plotted concurrent changes in total renal blood flow and renal arteriolar

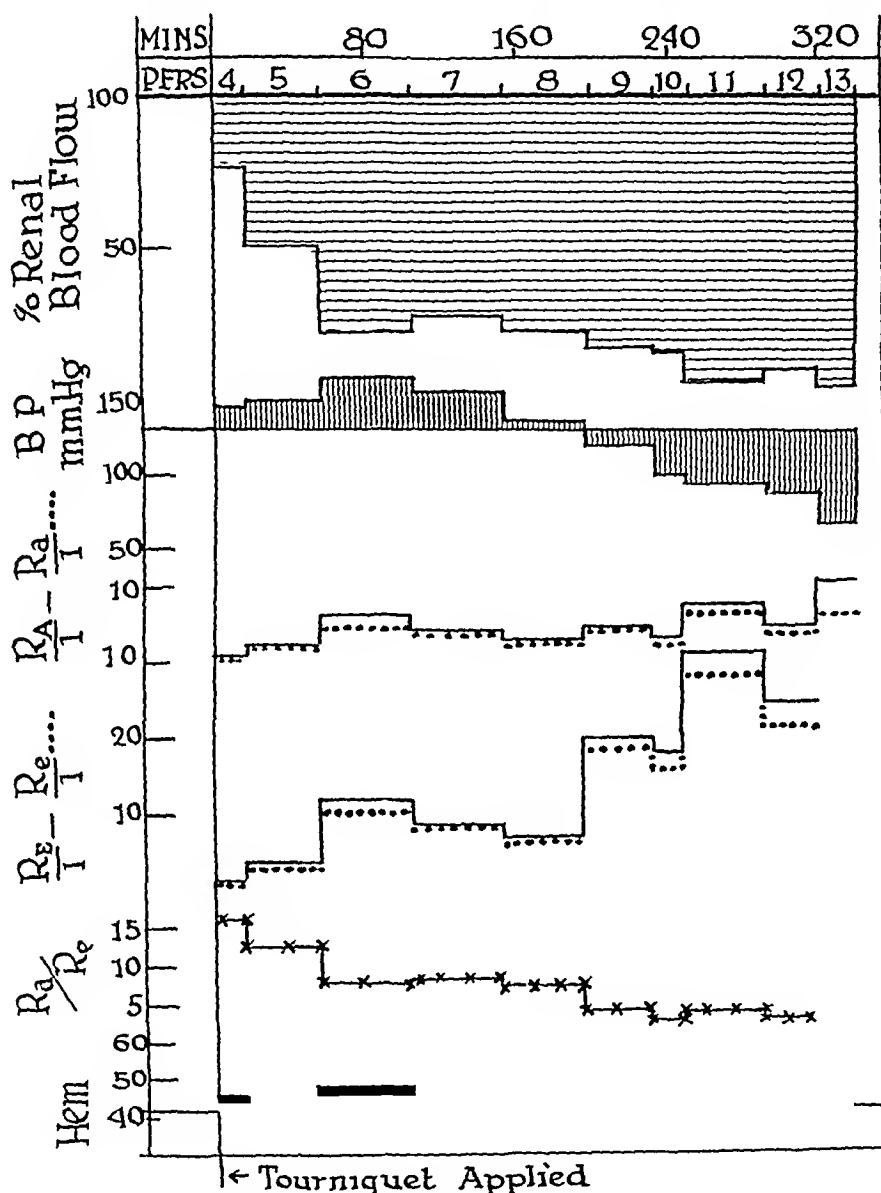


CHART 4.—Effect of tourniquet application on total renal blood flow, blood pressure (B P mm Hg) calculated renal resistance and hematocrit index in a normal dog with subcutaneously explanted kidney. The values of resistance (R) are shown as ratios of the control level which is taken as equal to 1, R_A , total afferent arteriolar resistance, R_{A-I} , the same corrected for changes of blood viscosity, R_E , total efferent arteriolar resistance, R_{E-I} , the same corrected for viscosity. The ratio R_A/R_E expresses the relative changes of arteriolar resistance proximal and distal to the glomeruli. Hem = hematocrit index.

resistance the latter calculated by the method of Lampert (1943) and considered in relation to the control level.

It might be supposed that a significant factor in this resistance to blood flow might lie in the viscous resistance due to erythremia (increased hematocrit index). That this is not a large element in the renal ischemia is shown in those experiments in which erythremia was abolished by splenectomy at least until the tourniquets were released (Chart 3). In passing

it should be noted that this effect of splenectomy extends and confirms the observations reported by Taylor and Page (1943). Lamport (1943) has proposed a nomogram by which the relative influence of viscous resistance due to changes in hematocrit index and plasma protein content may be estimated, and he suggests that this factor be applied to calculated renal arteriolar resistance, with the advantage that the values of apparent arteriolar resistance thus determined represent only the changes due to alterations in the blood vessels. We applied this correction to the values obtained in two experiments (Nos. 3 and 6) and, as shown in Chart 4 (from Experiment 3), found that erythremia accounted for only a small fraction of the resistance which developed in the renal circulation. We must, then, conclude that the increased renal resistance to blood flow during the onset of shock is the result of actual vasoconstriction. The calculations made both from Experiments 3 and 6 indicate that this resistance develops predominantly in the glomerular efferent arterioles.

Such a renal vasoconstriction might develop during the onset of shock on the one hand by operation of nervous influences as from pain at the site of tourniquet application and in swelling limbs, or, reflexly, from hypovolemia or, on the other hand, it might be due to the activity of humorally circulating vasoconstrictor substances.

That the renal nerves are not the predominant influences in the increased renal vascular resistance is shown by experiments in dogs subjected to renal denervation, both splenectomized (Chart 3) and nonsplenectomized (Experiment 2, above). However, it is noteworthy that renal plasma flow (from diodast clearance) did not decrease in these to the very low levels of 25 per cent of the control which was observed in normal dogs (Charts 1 and 2). The fact that blood was transfused during the experiments shown in Chart 3 does not alone explain the partial maintenance of renal perfusion during tourniquet application, for the infusion was very slow. Further, no infusion was given at this phase of Experiment 11 and here, the reduction of blood flow prior to release of the tourniquets was even less marked than in the group to which blood was given. Neurogenic renal vasoconstriction, possibly the result of pain, is, as are hypotension and hypovolemia, a factor in the genesis of renal ischemia during the onset of shock. But it is not the important factor, for there remains a reduction of renal plasma flow to about 50 per cent of the control levels when the combined influences of renal nerves of erythremia and, in large measure, of hypotension and hypovolemia are excluded respectively by renal denervation, splenectomy and blood transfusion (Chart 3).

There remains only the probability that most of the renal ischemia, with which we are here concerned, is due to the release into the blood of a humorally circulating vasoconstrictor material. Such a "peripheral vasoconstrictor substance" appears in plasma during procedures which cause shock (Page 1943), and it was shown to develop in plasma during six of seven experi-

ments of this report. Interestingly, the only dog in whose plasma it did not develop, *viz*, the one suffering from renal hypertension, also showed only a slight depression of renal plasma flow in most periods and, because of the increase in hematocrit, an actual rise of renal blood flow in some. Similarly, although no determinations of vasoconstrictor substance were made in Experiment 13, the absence of renal vasoconstriction in the animal whose limbs had been wrapped in plaster bandages before applying the tourniquets suggests that formation of the vasoconstrictor material had been inhibited by this procedure. Katz, Shleser, Asher and Perlow (1942) have observed a preventative action of limb encasements on shock due to the analogous procedure of venous occlusion, although they attributed this effect entirely to the prevention of loss of blood volume, while our experiment with the limb encasements suggests that failure of formation of vasoconstrictor substance may also be concerned. Indeed, circulatory depression due to release of this substance should, it seems to us, be reckoned among the harmful effects of tourniquets which, of course, include pain and sudden loss of blood volume (Wilson and Roome, 1936). In this connection, the observations of Blalock (1943) on the presence of a toxic substance in the thoracic lymph of dogs with injured hind legs might be cited, although no evidence is available to establish a relationship between Blalock's "toxic products" and the "peripheral vasoconstrictor substance" of Page. Duncan and Blalock (1943) have recently confirmed the widely held clinical view that release of a tourniquet long applied to an injured extremity is dangerous and often lethal. The systemic activity of "vasoconstrictor substance" probably enters into this effect.

The mechanism of the decrease in diodrast extraction ratio during circulatory depression after tourniquet release is not clear. We have observed a similar change during the renal circulatory adjustments which follow hypotension due to bleeding (Corcoran and Page, 1943) and the cause of the abnormality seemed to lie in a change in the equilibrium between plasma and renal interstitial fluid. In the present experiments, other factors, such as arteriovenous shunting or renal epithelial injury might also be adduced. Whatever its nature, this depression of diodrast extraction ratio has the effect that diodrast clearance no longer measures renal plasma flow as well as it normally does or as it did during the period when the tourniquets were still in place. Thus, interpretation of diodrast clearance as the equivalent of renal plasma flow is unwarranted after tourniquet release or analogous injury, as, also, after severe and repeated hemorrhage. Further, the resultant decrease of diodrast clearance in ratio to inulin clearance also alters the significance of filtration fraction, which cannot remain as an expression of relative levels of intraglomerular pressure or the equivalent of inulin extraction ratio. An increase of filtration fraction after severe injury is not always evidence of increased intraglomerular pressure, although such may develop. When intraglomerular pressure increases after injury, it may be because of efferent arteriolar constriction as in Experiment 3 (Chart 4), or

when it fails to appear it may be because the different constriction was accompanied by systemic hypotension (as in Experiment 6)

A few deductions may be made from the clinical point of view. First and in accord with clinical impressions we note that the renal resistance which develops during the tissue of tourniquet application is more intense than the resistance which slowly appears after severe and repeated bleeding (Corcoran and Page 1943) where the tissue injury is presumably milder and more diffuse. Second fear of interfering with blood flow as the result of increased viscous resistance due to erythremia is probably unwarranted under most circumstances, so that transfusion of blood should not be delayed because plasma otherwise desired, is temporarily unavailable. Third with reference to "traumatic anuria," i.e. the persistent and often recoverable loss of renal function which may follow crushing injuries or circulatory obstruction (for review see Editorial Brit Med Jour., 1942) the complete recovery seen in Experiment 1 (and in other similar experiments shortly to be published) indicates that tourniquet application alone does not satisfactorily reproduce this type of renal injury, nor cause lasting depression of excretory function. Indeed sections of the kidneys of two of our dogs after death which had ensued from four-hour application of tourniquets, did not have the appearance of early "traumatic anuria" described by Bywaters and Dible (1942). However, the severe hemodynamic changes which do appear in the kidney during and after tourniquet release are sufficient explanation for subsequent transient signs of renal irritation without excretory failure such as were observed after limb crushing by Duncan and Blalock (1942). Our failure to reproduce the syndrome of traumatic anuria by a procedure which depends upon massive swelling of limbs suggests also that the explanation of the syndrome as the simple result of excessive fluid loss is unsatisfactory. Finally pending a full explanation, consideration should be given the view that traumatic anuria depends upon myoglobin aggregating in and plugging or poisoning renal tubules (Bywaters and Beall, 1941) and with this view in mind, certain points arising from our experiments may be recalled. Thus (a) the depressed renal blood flow and filtration rate of severe injury would largely tend to prevent excretion of myoglobin from plasma and its consequent deposition in tubules until renal excretory function had been improved by treatment of shock. Therefore (b) measures of urinary alkalinization and diuresis such as those proposed by Bushby, Hart, Kerwick and Whitby (1940), might well be adopted before transfusion of blood or plasma in patients with crushing injuries. However (c) since renal function is depressed during the onset of shock so that myoglobin may tend particularly to injure tubules at this time measures for the relief of shock should themselves tend to prevent renal failure.

SUMMARY

Onset of shock due to the four-hour application of partially occluding hind limb tourniquets to anesthetized dogs causes a marked depression of

renal function, which is the result of reduction in renal blood flow. The factors which may enter into this decrease of renal blood flow are (1) decreased arterial pressure, and (2) increased renal resistance to the flow of blood. Hypotension, however, is only a minor and inconstant element, increased renal resistance is much more important. Among the causes of increased renal resistance, blood viscosity due to a rise of hematocrit index is not significant, for splenectomy, which prevents the increase of hematocrit, does not interfere with the reduction of renal blood flow. Although renal vasoconstriction of nervous origin is a greater factor than viscous resistance, it, too, accounts for only a small proportion of the renal ischemia which follows tourniquet application and release as is shown by renal denervation. The decrease in renal blood flow which occurs while limb tourniquets are in place when these factors are excluded, *i.e.*, in dogs previously subjected to renal denervation and splenectomy, and in which arterial pressure and blood volume are maintained by blood transfusion during the experiment, seems to be due to some humorally circulating vasoconstrictor substance. Such a material was demonstrable in the plasma of several animals in which its presence was associated with increased renal resistance, predominantly at the glomerular efferent arterioles. With injury, as after the release of tourniquets, diiodast renal extraction ratio may be depressed, so that normal interpretations cannot be given to changes in plasma diiodast clearance and filtration fraction. The renal vasoconstriction associated with the onset of shock serves to explain transient signs of renal irritation which may follow injuries. Although it may play a part in the genesis of "traumatic anuria" ("crush syndrome") it alone does not reproduce this state.

CONCLUSIONS

- 1 The depression of renal function during the onset of shock due to partially occluding tourniquets is due to a decrease of renal blood flow which is only in a minor and inconstant measure the result of decreased arterial pressure.
- 2 This decrease of renal blood flow is due almost wholly to increased renal vascular resistance, into which increased blood viscosity enters only in small degree, the increased resistance being rather due to vasoconstriction, predominantly affecting the glomerular efferent arterioles.
- 3 Although nervous stimulation, presumably as the result of pain, causes a small measure of this vasoconstriction, much the larger fraction is independent of the renal nerves and, by exclusion, of humoral origin.
- 4 This humorally-arising renal vasoconstriction is associated with the appearance in plasma of a vasoconstrictor substance to whose activity it is therefore attributed.

We acknowledge the skilful assistance of Mr Truman Woodmansee, B.S.

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PRIMARY OSTEOGENIC SARCOMA OF THE BLADDER

COMPLETE REVIEW OF SARCOMATA OF THE BLADDER

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ALTHOUGH PRIMARY SARCOMA OF THE BLADDER is an infrequently encountered tumor, we have been able to collect 151 cases from the literature up to 1943. Many histologic types have been reported, but in terms of modern histogenetic classifications, these would be reduced to angiosarcoma, fibrosarcoma and fibromyxosarcoma, malignant lymphoma, leiomyosarcoma, neurogenic sarcoma, rhabdomyosarcoma, chondrosarcoma and osteogenic sarcoma. Undoubtedly, some of the more undifferentiated tumors reported as round cell and spindle cell sarcomata, *etc*, represent anaplastic carcinomata, or would be more properly classified with the fibrosarcomata. Of the various types, the bone-producing tumors are the rarest and most peculiar from a histogenetic point of view. Eight cases of primary malignant bladder tumors producing bone or cartilage have been collected from the literature (Table I), and it is with this group of tumors that this paper is primarily concerned.

In 1856, Ordonez¹ recorded the first instance of a malignant bladder tumor containing elements of cartilage or bone. His case, occurring in an "old man," is reported as a "chondroma" but is described as "an infiltrating tumor of the bladder composed of a fibrous tissue matrix, containing large numbers of cartilage cells." The bladder was filled with a transparent yellowish-brown gelatinous substance. Further clinical or pathologic details are not given in his report, which deals chiefly with the histologic structure, but the tumor would probably be more accurately classified as a chondrosarcoma.

The second case was reported by Shattock² in 1887, who reported a tumor in a 55-year-old male located in the region of the trigone about the right ureter, and productive of hematuria and dysuria for four years. On surgical excision, the tumor was covered by mucous membrane and was in part papillary in form. Histologically, it is described as being composed of cartilage and of a "sarcoma tissue of a spindle and mixed cell variety." The patient died nine months after the operation, and at autopsy showed a large soft growth, two inches in diameter, encroaching on the bladder from the base. The right ureter passed through the middle of the growth and was dilated. The bladder was diffusely infiltrated by the tumor which at this time was found to be a "round-cell sarcoma" and contained no cartilage. There were also multiple papillomatous growths in the bladder. Shattock records the case as one of "chondrifying sarcoma and multiple papillomata." From the material available, any other classification under current terminology is not warranted.

TABLE I
MALIGNANT OSTEOGENIC TUMORS OF THE URINARY

Date	Author	Sex	Age	Symptoms	Location	Author's Diagnosis	Modern Diagnosis	Metastases	Course
1856	Ordóñez ¹	M	Old	?	?	(chondroma)	(chondrosarcoma)	None	Died
1887	Shattock	M	55	Hematuria dysuria—4 yrs	Triangle over right ureter	(chondroma)	(chondrosarcoma)	None	Died—9 mos
1899	Beneke	M	72	Hematuria weeks	Triangle over left ureter	(chondrosarcoma)	(osteogenic sarcoma)	None	Died—8 wks pyelonephritis
1905	Heisler ¹	?	11	?	Posterior bladder wall	(fibro-sarcoma into myo-epithelium)	(chondrosarcoma)	?	?
1908	Ischer ²	F	62	Hematuria dysuria obstruction—5 mos	Base of bladder on right	(osteoid chondrosarcoma)	(osteogenic sarcoma)	Local pleuritic empyema	Died—4 wks Cachexia hydronephrosis
1913	Ried ³	M	57	Hematuria dysuria obstruction—6 mos	?	(chondrosarcoma)	(osteogenic sarcoma)	Invasion of rectum	Died—1 mo Cachexia
1929	Wright-Smith ⁴	M	47	Hematuria dysuria frequency—5 wks	Superior surface	(osteogenic sarcoma)	(osteogenic sarcoma)	None	Died—6 days
1938	Droschl ⁵	M	67	Weight loss—1 yr frequency—6 wks	Triangle over right ureter	(osteogenic sarcoma)	(osteogenic sarcoma)	?	Died—1 day post-operative
1943	Crane & Tremblay	M	69	Hematuria—6 mos Dysuria—2 mos	Triangle over left ureter	(osteogenic sarcoma)	(osteogenic sarcoma)	Local pelvic abscess abdominal wall metastases transverse colon metastases lungs	Died—41 mos Cachexia urinary pyelonephritis

These first two recorded cases dealt with tumors containing cartilage. Then, in 1899, Beneke³ reported a case of osteochondiosarcoma, this being the first one described as producing bone. A 72-year-old male with a history of hematuria of a few weeks' duration, at operation showed a pedunculated tumor, the size of a "small apple" originating at the lateral edge of the trigone and covering the mouth of the left ureter. The tumor was excised. Grossly, it was mushroom in shape, hard and showed trabeculations having the consistency of bone. Histologically, it showed much osteoid tissue and in some areas bone with osteoclasts. Other portions were very cellular, most of the cells being spindle-shaped. Areas of hyaline cartilage shading into zones of active bone formation and bone marrow were also present. The patient died eight weeks after operation of pyelonephritis. At autopsy, there was invasion of the bladder by the tumor which showed the same histologic structures described above. Skeletal muscle fibers were also present. Only local extension metastases occurred. There is no question that this tumor belongs in the group of osteogenic sarcomata.

In 1905, Heisler⁴ reported a "fibro-edemato-myoenchondroma" occurring on the posterior bladder wall of a one and one-half-year-old infant. This case was cited by Fischer, but we have been unable to find the original article.

Fischer,⁵ in 1908, reported the first case of an osteogenic sarcoma with distal metastases. This was a 62-year-old female with a five-month history of hematuria, dysuria, urinary obstruction, and emaciation, who died following a cystotomy. At autopsy, a tumor 7.0 x 5.0 x 5.5 cm was found at the base of the bladder on the right side. Grossly, it was encrusted, hard and white. Microscopically, it contained bone, cartilage and fibrous tissue elements. Metastases were present in the pleura, omentum and about the right ureter, and all of these presented the same histology as the original tumor. There were also marked bilateral hydronephroses and hydronephrosis and a bronchopneumonia. Fischer reported this as an osteochondiosarcoma.

Ried,⁶ in 1913, published a case of chondromyxosarcoma in a 57-year-old male with a six-months' history of hematuria, dysuria and increasing urinary obstruction. At operation, a hard tumor completely filling the bladder was found. Microscopically, it showed a varied cellular structure interpreted as sarcoma with areas of osteoid material, osteoclastic giant cells and areas resembling osteitis fibrosa cystica. At autopsy, four months later, the tumor had diffusely infiltrated the bladder wall and rectum, but there were no other metastases. This tumor, we believe, can also be classified as an osteogenic sarcoma.

In 1929, Wright-Smith⁷ encountered at autopsy a bladder tumor in a male, age 47, with a history of hematuria, dysuria, nocturia and frequency of five weeks' duration. The tumor projected into the bladder from the superior surface. Histologically it was composed of spindle-shaped cells and many areas of embryonic cartilage and showed patchy calcification and

many large giant cells (\approx osteoclasts). The case is reported as a teratogenous sarcoma but may again be classified as an osteogenic sarcoma.

The last case was recorded, in 1938, by Droschl⁶ as an osteoid sarcoma occurring in a 67-year-old male with a history of loss of weight for one year and frequency and urgency for six weeks. At operation a pedunculated tumor, the size of an apple, was found arising from the region of the trigone and overlying the right ureter. Microscopically, it was composed of closely packed spindle cells ramifying between which were bands of osteoid material. Multinucleated giant cells (\approx osteoclasts) were numerous. Many blood vessels showed invasion by the tumor cells. The patient died one day after operation and an autopsy limited to the genito-urinary tract showed no local metastases.

To these cases we are adding another which is the first to have been studied chemically and histochemically as well as histologically.

Case Report—I. W. B., a 69-year-old married white fireman, came to the hospital, with a chief complaint of hematuria. His past history was entirely negative save for (1) typhoid fever 25 years ago, and (2) fracture of right lower extremity five years ago. The family history, systemic review and personal history were non-contributory.

Present Illness Six months before his first admission on January 13, 1943, he noted the onset of gross hematuria. He passed blood throughout micturition. He consulted his physician who prescribed pyridium. Following administration of this drug the gross hematuria disappeared, and the patient was symptom-free during the next three months. However, during the two months before being admitted to the hospital he noted hematuria on five separate occasions. The hematuria was now associated with marked dysuria especially toward the end of micturition and on the last two occasions, he passed small blood clots.

Physical Examination The patient was a well-developed and well-nourished white male. Temperature 99, pulse 84, respirations 20, blood pressure 170/80. The positive physical findings included: Edentulous upper and lower jaws. Lungs—clear to percussion and auscultation save for rales at both bases posteriorly. Heart—no abnormalities except for distant heart sounds. Abdomen—entirely negative. Bladder not distended. Extremities—slight angular deformity just above right angle, at site of previous healed fracture. Rectal—prostate slightly enlarged, especially the right lobe and presents two irregular nodular areas about 0.5 cm. in diameter. There is no impression of fixation of the gland and its consistency though firm is not stone hard. No rectal masses were felt nor was there any blood on the examining finger.

Progress The patient was catheterized after voiding and two ounces of grossly bloody urine obtained. The next day on cystoscopy some difficulty was encountered in passing the instrument through the bladder neck but after some manipulation toward the right, it entered the cavity of the bladder. A large, irregular grayish-yellow mass was seen to the left of the midline and lying over the bladder floor. There was no visible viable tissue and, on motion of the cystoscope against this mass, a grating sensation was felt. The diagnosis of a large vesicle calculus was made, and on the second hospital day, a suprapubic cystotomy was performed. On opening the bladder, an oval, lobular, firm tumor, 10 cm. in diameter, was encountered. The tumor was attached to a stalk 5 cm. in diameter at its base and having its origin partially covering the left ureteral orifice. The surface of this tumor was covered with what appeared grossly to be phosphatic deposits. The tumor was removed by dissection and the base thoroughly cauterized. Thorough exploration of the bladder revealed no other abnormalities.

save for an hypertrophied prostate. The patient's postoperative course was not remarkable. On the tenth postoperative day, a second-stage prostatectomy was performed. The gland proved to be markedly adherent to the capsule and was enucleated with difficulty. His postoperative course following the second operation was also uncomplicated.

The tumor which had been removed from the bladder was reported by the pathologist to be an osteogenic sarcoma, and the prostatic tissue which was removed

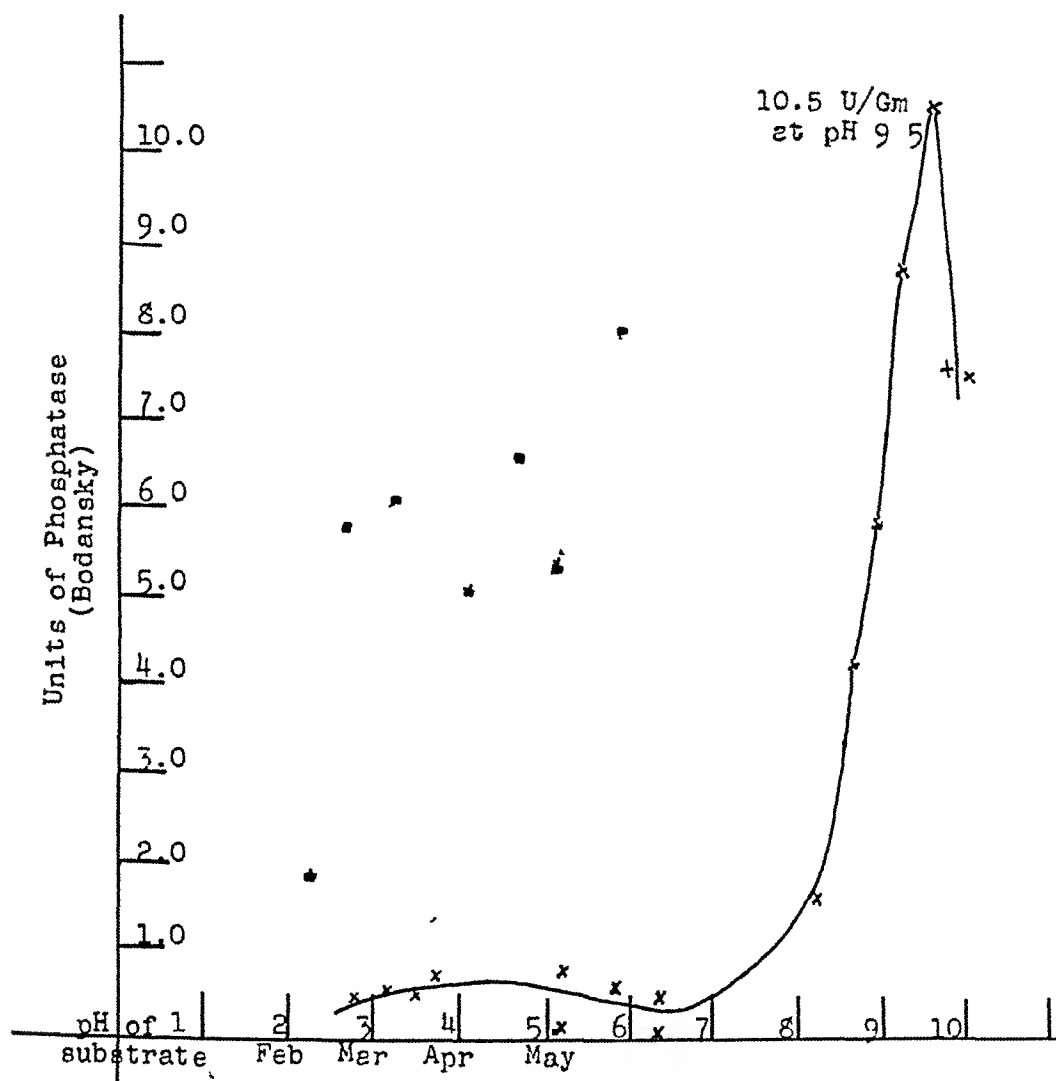


FIG. 1.—The solid line shows the phosphatase content of the tumor per gm of tissue with a substrate of various pH levels. Determinations on the original tumor and the metastases are identical. The dotted line shows the serum alkaline phosphatase during life. For this curve each gradation of the abscissa equals one month.

revealed chronic prostatitis, benign adenomatous hyperplasia and two small microscopic areas interpreted as adenocarcinoma. Radiographs of the chest, shoulder and pelvic girdles, and lumbar spine failed to reveal any evidences of metastases. An intravenous urogram showed that the kidneys were slow in excreting the dye. No definite renal pelvis could be outlined on the left side, but the right renal pelvis appeared normal. Following this, repeated blood chemistry studies were made. The serum calcium ranged between 11.4 and 13.0, and the serum phosphorous between 2.9 and 3.3. The total serum proteins were 5.9, albumin 2.7 and globulin 3.2. The urea nitrogen averaged 20 mg. The urea clearance test revealed a kidney function of 19.8%. The Mosenthal test showed a fixed specific gravity ranging from 1.013 to 1.016. The blood Wassermann, Kahn, and Hinton tests were negative. A urine culture revealed a heavy growth of *B. subtilis*. The blood count which on admission had shown 10.4 Gm (70%) hemoglobin

and 4,100,000 red blood cells had dropped to 80 Gm (53%) hemoglobin, with 4,100,000 red blood cells at the end of his fourth week in the hospital. The serum alkaline phosphatase, which had ranged between 13 and 17 immediately after removal of the tumor, rose to 59 (Fig. 1) on the 34th day after the first operation. A cystogram (Fig. 2) done at this time showed a filling defect in the left side of the bladder wall. Cystoscopy revealed a well-funnelized bladder neck. The right ureteral orifice appeared normal. The left ureteral orifice could not be seen. On the left lateral wall posteriorly, there was a rounded, elevated smooth mass 2.5 cm in diameter and 1.0 cm in height and adjacent to this another mass 1.5 cm \times 0.5 cm both having the appearance of



FIG. 2.—Cystogram showing abnormal shape of bladder and filling defect on the left

new growths. The alkaline phosphatase continued to range between 55 and 59 up to the time of the patient's discharge from the hospital on February 25, 1943, on his 43rd hospital day. His general condition at the time of discharge was good, and he was symptom-free.

One week after leaving the hospital, he developed a painful swelling of his right testis. At the same time, he began to have urinary frequency, dysuria, urgency and incontinence of urine of a mild degree. On March 8, 1943, he entered the hospital for the second time. Physical examination at this time revealed the following additional findings: A well-healed midline suprapubic scar, a swollen, tender right testicle. Roentgenograms of the chest, shoulder and pelvic girdles, and lumbar spine were repeated, and still failed to show any evidence of metastases. A radiograph of the skull, however, showed an area of rarefaction 4.5 cm in diameter in the right

parietotemporal region and several small punched-out areas scattered throughout the skull. A cystogram of the bladder revealed a filling defect involving nearly all of the left hemisphere of the bladder. Cystoscopy showed an irregular infiltrating tumor which entirely filled the left half of the bladder. Several pieces of tissue were taken with a biopsy forceps and again showed an osteogenic sarcoma. The serum alkaline phosphatase at the time of his second admission was 60.

On March 29, 1943 a subcutaneous nodule 1.5 cm in diameter, which had first made its appearance one week before and had been increasing rapidly in size, was biopsied, and the specimen reported to be osteogenic sarcoma. The patient continued progressively downhill. One month before his death, the suprapubic scar broke down and he began to drain urine through the opening. Two other subcutaneous nodules made their appearance, one above and one below this opening. His urea nitrogen which had been 35.0 and creatinine 3.2 at the time of his second admission gradually rose to 80.0 and 5.2, respectively. He became progressively more drowsy and finally comatose two days before his death. His alkaline phosphatase was 80 at this time. The acid phosphatase ranged from 0.5 to 0.6 on repeated determinations. He had a generalized convulsion 12 hours before his death. His respirations became labored and his pulse weak, and he finally died on May 24, 1943, four and one-half months after his operation, and ten and one-half months after onset of symptoms.

PATHOLOGIC STUDIES

The original tumor (S 43-48) was removed in pieces varying from 0.6 to 6 cm in diameter and weighing 104 Gm. Externally, the fragments were rough and irregular and had a brown, encrusted surface. The cut surfaces were white, hard, and gritty. Microscopically (Fig 4), multiple sections showed irregular anastomosing bands of a dense, acellular, eosinophilic material between which were single or small groups of polyhedral to spindle-shaped tumor cells with large, central, oval to round, vesicular but hyperchromatic nuclei. At many points, these cells were arranged along the margins of the intercellular substance like osteoblasts. Large osteoclastic giant cells were present, and there were also groups of cartilage cells. Mitoses were numerous and the tumor could be seen invading capillaries. A crystal violet stain for amyloid was negative. Mallory's aniline blue and phosphotungstic acid-hematoxylin stains were negative for intracellular fibrils, and Weigert's stain for elastic tissue showed none within the tumor. Subsequent biopsies of the bladder tumor (S 43-209) and incisional metastases (S 43-275) occurring during life showed an identical histologic structure and were similarly interpreted. *Pathologic Diagnosis* Osteogenic sarcoma.

The prostate (S 43-84) weighed 10 Gm and showed a typical benign adenomatous hyperplasia, chronic prostatitis, and two small foci of irregular arrangement of the glands interpreted as microscopic foci of adenocarcinoma.

The autopsy (A 43-1591) was performed about 30 minutes after death, only the positive findings are given. Inspection. The body was that of an emaciated, adult, white male. The abdomen presented two nodules located in the midline just above the symphysis pubis. Each measured about 5.5 cm in diameter, was firm, and covered by a flattened, tense, bluish skin. Between the two nodules was an opening 0.3 cm in diameter which communicated with the bladder. The right lower extremity presented a deformity of the tibia 3 cm above the internal malleolus which was a hard, bony thickening measuring 4 x 2 cm at the site of an old fracture. Only the inguinal lymph nodes were enlarged and these were all less than 1 cm in diameter. Peritoneal Cavity. The pelvis contained a large mass, about 18 x 10 cm, continuous with the bladder and the skin nodules. There were no adhesions between the mass and any abdominal organs, and it did not invade the rectum. Thorax. About 10 cc of fluid was present in each pleural cavity, and the pleural surfaces of each lung contained multiple hard white tumor nodules, 0.5 to 2 cm in diameter. Heart. Negative.

Aorta Moderate atherosclerosis of the abdominal portion **Lungs** The left weighed 325 Gm, the right 450 Gm. Each showed multiple pleural and parenchymal, circumscribed, hard, white tumor nodules 0.5 to 2 cm in diameter. **Spleen** Negative. **G.I. Tract** There was a Meckel's diverticulum, 5 x 3 cm, of the ileum, and a few small (0.2 cm), white nodules in the mesentery at the edge of the small bowel. **Pancreas and Liver** Negative. **Kidneys** The left weighed 80 Gm, the right 150 Gm. Each showed a marked dilatation of the ureter and pelvis and contained a yellow, purulent material. The surfaces were irregularly granular and showed flat depressed scars and small, yellow abscess nodules 0.1 to 0.2 cm in diameter. On the cut surface the pyramids were indistinct. **Adrenals** Negative. **Bladder** (Fig 3) Measured about 12 cm in diameter and was entirely filled by a grayish-green, cauliflower-like growth growing from a broad base covering most of the posterior and superior bladder

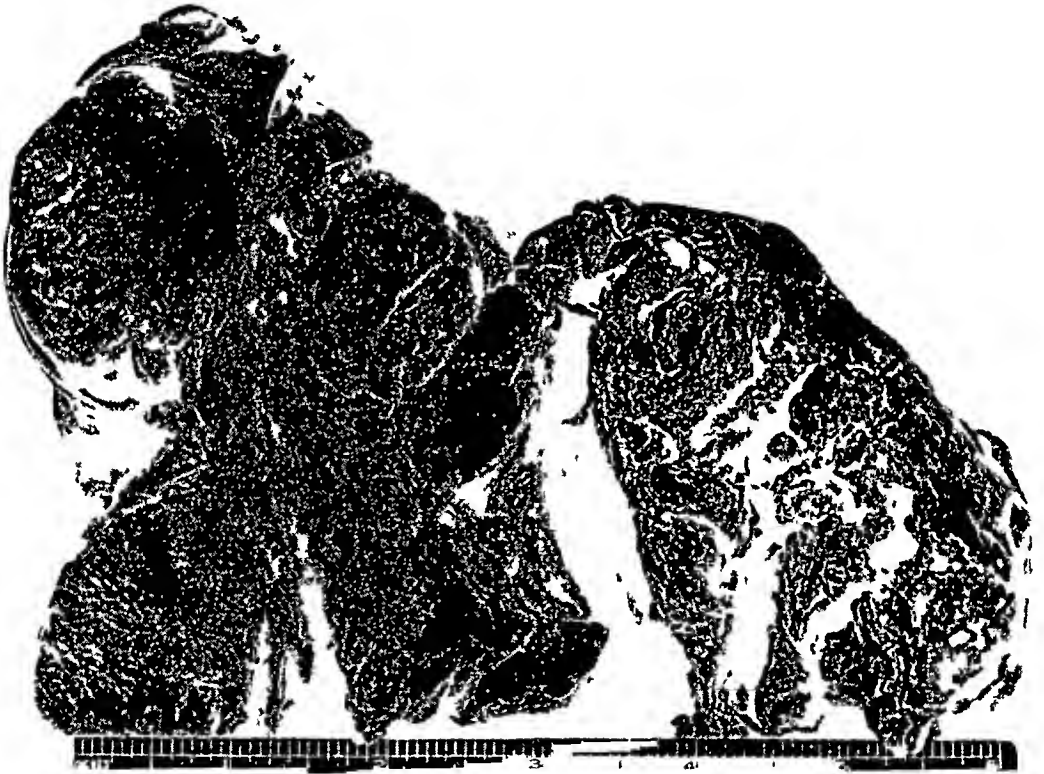


FIG 3.—Gross specimen hemisected longitudinally. The bladder with the fungating mass, lies to the right. To the left is the anterior bladder wall and the huge mass of tumor invading the abdominal wall. Skin and pubic hairs may be seen at the left margin.

walls. On section, the mass was hard, gritty, firm and white. The posterior bladder wall was thickened, measuring 3 cm, and was also firm, white, and gritty, being diffusely infiltrated by tumor tissue. The anterior bladder wall was 0.4 cm thick, gray-green and necrotic. The ureters opened directly into the tumor mass and were markedly constricted by it. **Genital Organs** Negative save for surgical absence of the prostate. **Bone Marrow** Negative. **Lymph Nodes** Negative, none showed any tumor metastases. **Head** The skull showed no evidence of metastatic tumor and the brain was negative.

Microscopic Tumor Sections of the bladder tumor, bladder wall infiltrated by tumor, skin nodules, mesenteric and pulmonary metastases all showed a similar histologic picture identical with that described in the original surgical specimen (S 43-48). The tumor cells resembled osteoblasts and there was much osteoid material, osteoclastic giant cells and cartilage (Fig 4). Mitoses were numerous. Stains for alkaline phosphatase (Fig 5) showed large amounts in the cells and intercellular tissue of the more

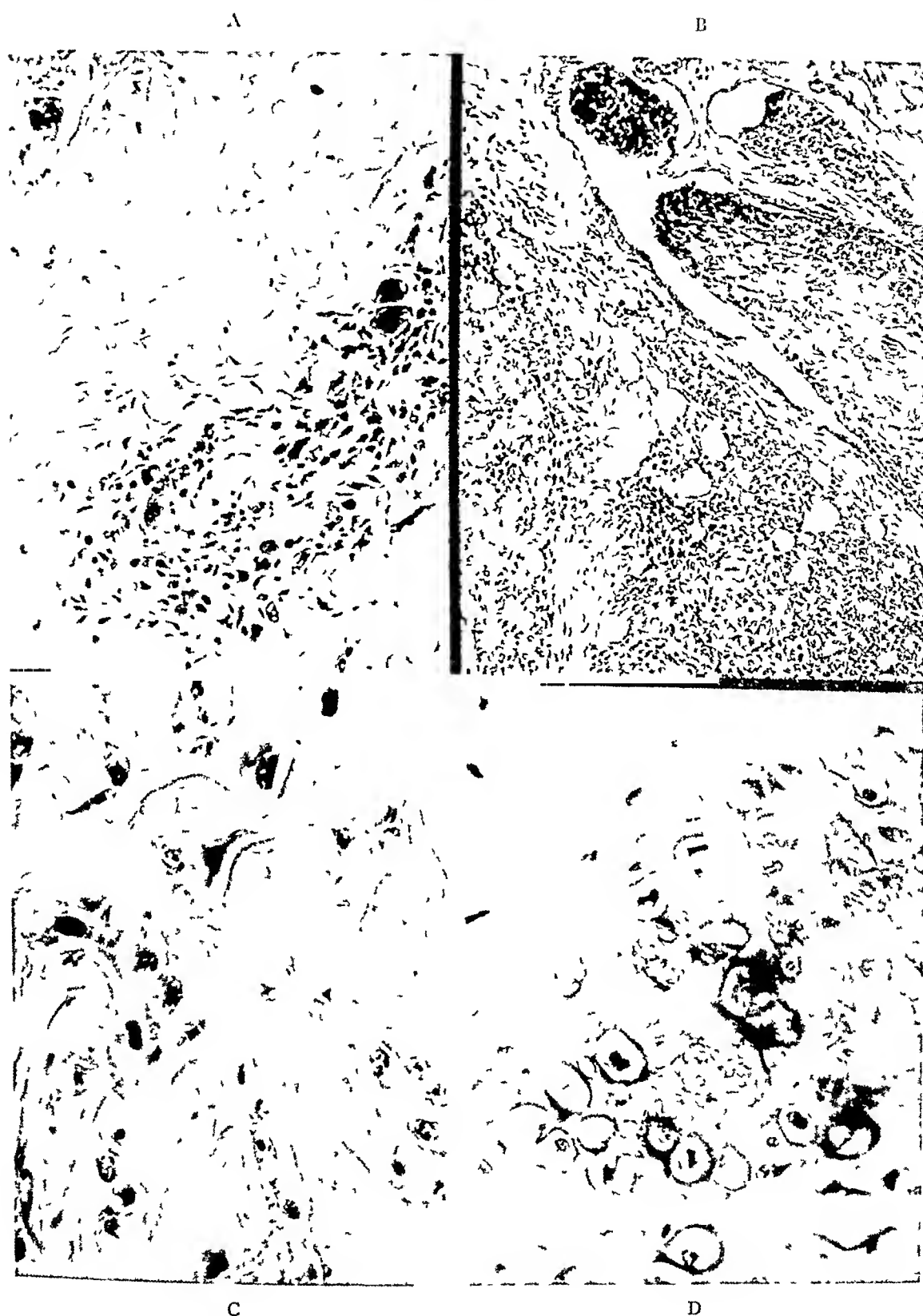


FIG 4—(A) Adult bony portion of primary tumor showing osteoid material, osteoblasts and osteoclastic giant cells. Phloxine methylene blue ($\times 130$)
 (B) More cellular portion of a local extension of the primary tumor showing blood vessel invasion. Phloxine methylene blue ($\times 110$)
 (C) Osteoid zone of primary tumor showing osteoblasts and intercellular substance. Phloxine methylene blue ($\times 335$)
 (D) Cartilaginous zone of primary tumor showing large cartilage cells. Phloxine methylene blue ($\times 335$)

cellular portions and none in the osteoid material. Stains for acid phosphatase were negative. Kidneys showed interstitial scarring and lymphocytic infiltration, with compression of the tubules, many of which contained colloid-like casts. Some contained masses of bacteria and neutrocytes. Meckel's Diverticulum contained gastric mucosa. Tibia and Skull Negative for tumor tissue.

Chemical Analysis H. Q. Woodard, Ph.D., of Memorial Hospital, N. Y. C. extracted the tumor and the metastases and determined the phosphatase activity at different pH levels (Fig. 1). In the acid range less than 6.5 units per Gm. were present but in the alkaline range there was a sharp increase to 10.5 units per Gm. at a pH of 9.5.

Anatomic Diagnoses Osteogenic sarcoma of the bladder with metastases to the abdominal wall, pelvic cavity, lungs and intestinal serosa, chronic cystitis, chronic pyelonephritis, bilateral pyonephrosis and pyoureter, vesicle sinus, Meckel's diverticulum with heterotopic gastric mucosa, aspermatogenesis of the testes, cysts of the choroid plexus, healed fracture of the right tibia, and moderate aortic atherosclerosis.

DISCUSSION—Here we have a malignant tumor, which both in the original and in the metastases is producing bone with polyhedral to spindle cells resembling osteoblasts, an osteoid stroma, osteoclastic giant cells and cartilage. From a purely histologic viewpoint it should be classified as an osteogenic sarcoma. This diagnosis is substantiated by the chemical extraction of the tumor showing little or no phosphatase activity in the acid range and a sharp rise in phosphatase activity in the alkaline range to a maximum of 10.5 units at a pH of 9.5 (Fig. 1). Such a curve of phosphatase activity has been found by Woodard,⁹ and by Woodard and Higinbotham¹⁰ only in the more cellular (rapidly growing) forms of osteogenic sarcoma. The diagnosis is further supported by the histochemical distribution of alkaline phosphatase occurring both intracellularly and intercellularly, as described by Gomori,¹¹ and by Kabat and Fuhr¹² in osteogenic tissues and tumors. Of final confirmatory value is the progressive rise in serum alkaline phosphatase during life (Fig. 1). It is of interest that following the first excision of the tumor when proliferating osteoblasts were minimal the serum alkaline phosphatase was low. Then as the tumor recurred and increased in size, the phosphatase values of the serum rose progressively, practically paralleling the recurrence of the tumor tissue. This is in accord with the observations of Franseen¹³ on primary bone tumors.

What is the origin of such tumors? Two possibilities have been suggested by previous writers.^{4,6} First that they represent a metaplasia of bladder mucosa, and, secondly that they are derived from embryologic rests of the wolffian body from which the trigone of the bladder develops. Sarcoma of the bladder is a rare tumor in itself and of the 151 cases collected from the literature only nine or six per cent may be called osteogenic. Considering the much greater frequency of carcinomata the question arises as to whether these bone-producing tumors are not examples of extreme metaplasia occurring in epithelial tumors. That they do produce bone must be admitted but if the cells are epithelial one would then have to accept the term 'osteogenic carcinoma'. Several items serve to add interest to the

OSIEOGENIC SARCOMA OF BLADDER

conjecture of the possible epithelial origin of the tumors Greenstein¹⁴ has shown that intestinal mucosa and the kidney of mice and the Jensen sarcoma and transplantable hepatoma of rats contain large amounts of alkaline

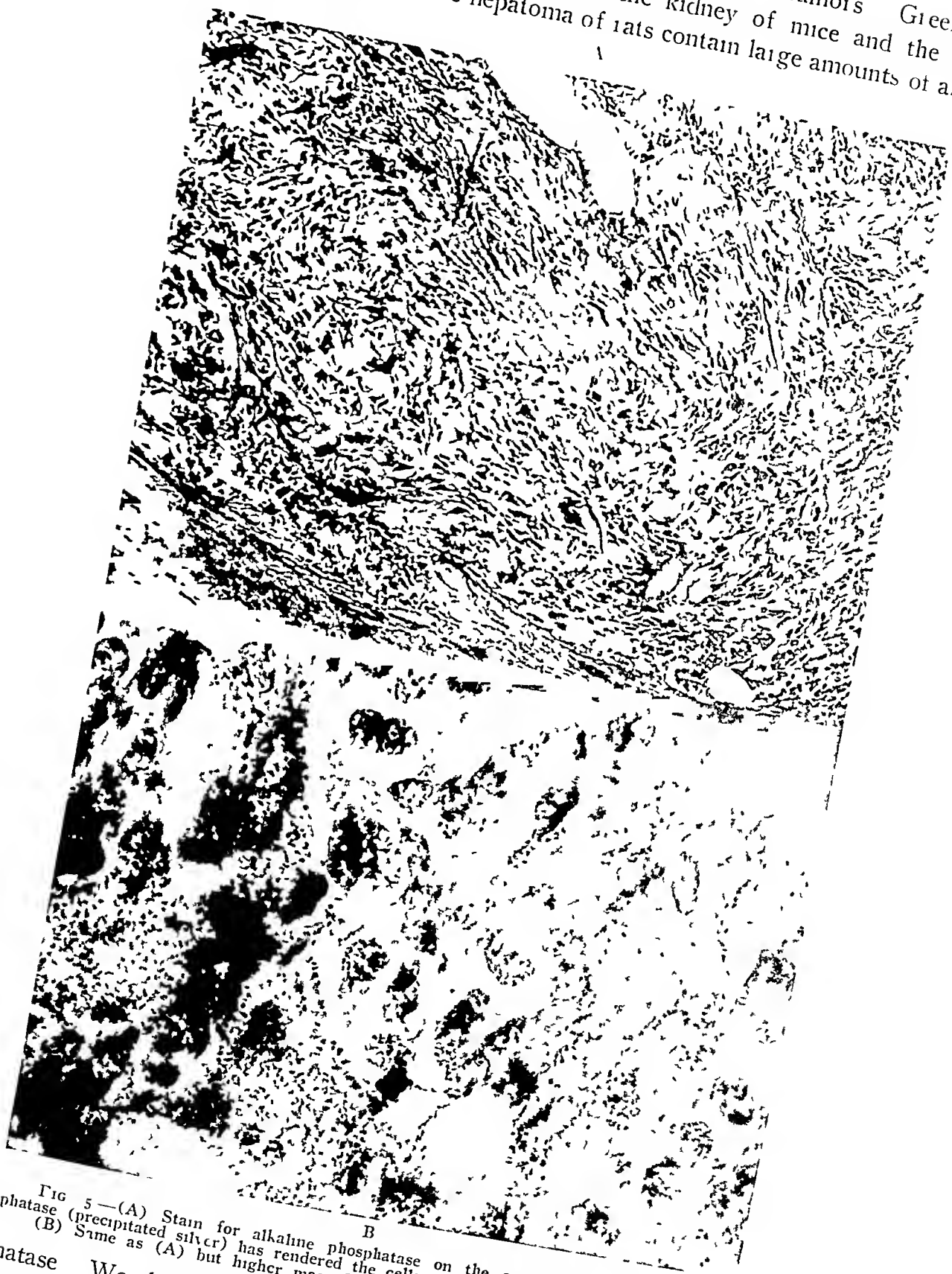


FIG 5—(A) Stain for alkaline phosphatase on the original tumor The phosphatase (precipitated silver) has rendered the cells into dark black masses (x 80)
(B) Same as (A) but higher magnification (x 700)

phosphatase Woodard¹⁵ has shown that the liver cancer produced in rats by the feeding of p-dimethylaminoazobenzene contains large amounts of

alkaline B-glycerophosphatase White, Dalton and Edwards¹⁶ have noted that these induced hepatomata frequently calcify However, in none of these instances is there a phosphatase content as high as that reported in osteogenic sarcoma Kabat and Furth¹² have described large amounts of phosphatase occurring in the epithelium of the renal pelvis and the bladder mucosa of mouse embryos, and this lessens the diagnostic value of the histochemical demonstration of phosphatase in regard to settling the question of the nature of the proliferating cells in these osteogenic tumors Since phosphatase plays an important rôle in bone formation, the possible derivation of such tumors from these phosphatase-rich cells must be considered However, this would entail the admission of the development of bone and cartilage from epithelial cells, other evidence for which is lacking both in normal tissues and tumors of the genito-urinary system in which the occurrence of bone is infrequent Chemical and histochemical determinations on epithelial tumors of the bladder will serve to clarify the subject

It is more plausible to assume that the phosphatase content of the epithelial cells may influence subsequent development of tumors derived originally from mesodermal elements Neuhof¹⁷ has shown that transplants of fat and fascia to the bladder of dogs ossify This, he interpreted, as metaplasia due to the stimulation of calcium salts derived from the urine This along with the infrequency of ossification of the epithelial tumors of the bladder suggests that the ossification is due to the stimulation of mesodermal elements Huggins¹⁷ has shown that bladder, ureter and renal pelvis epithelium stimulate the formation of bone about transplants made into certain parietal fascias (rectus sheath, fascia lata and subcutaneous tissue) and in muscle and synovial membrane in the dog This effect he attributed to the high calcium and phosphorous content in cysts developing at the site of the epithelial transplants and a greater permeability of the newly formed epithelium lining the cysts Urinary epithelial transplants into kidney, liver, spleen and the connective tissue wall of the bladder did not ossify and Huggins differentiated, on physiologic grounds the fibrocytes developing around transplants in these locations from those of fascia where ossification occurred This latter finding lends further support to the concept that osteogenic tumors occurring in the bladder of man develop from embryologic rests stimulated by both the phosphatase content of the urinary epithelium and its ability to cause high concentrations of calcium and phosphorous locally The frequent location of sarcomata of the bladder in and about the trigone (Table II) has been interpreted as evidence of their origin from remnants of the wolffian body from which the trigone is developed While only fifty per cent of the cases reported clearly indicate an origin in the region of the trigone fully half of the remainder also involved this region Numerous dermoid cysts containing skin, hair, teeth, bone, cartilage, *etc*, have also been reported in this location^{18, 19} The combined evidence would indicate that mesodermal elements derived from the wolffian body may persist in the region of the trigone and give rise to benign or malignant tumors of varied

OSTEOGENIC SARCOMA OF BLADDER

TABLE II

SHOWING THE AGE AND SEX DISTRIBUTION OF REPORTED CASES AND THE SYMPTOMS LOCATION OF TUMORS AND THE HISTOLOGIC TYPES OCCURRING AT VARIOUS DECADES*

Age in Decades	1-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	Not Given	Totals
Cases	M 19 F 11	6 3	6 3	8 7	12 6	22 11	11 4	9 2	1 1	9	93 48 151
Symptoms											
Hematuria	11	6	1	10	13	20	10	8	0	2	84
Dysuria	9	3	0	5	9	12	10	4	0	1	53
Frequency	13	2	0	7	8	9	7	4	1	2	53
Other (pain cystitis, mass)	16	1	5	4	5	11	8	4	1	0	58
Location											
About trigone and ureters	14	2	6	7	6	12	7	3	1	4	62
Elsewhere	13	7	2	6	12	9	6	5	1	1	62
Pathologic diagnosis											
Myo or leiomyosarcoma	3	2	0	2	1	4	2	3	0	2	19
Fibrosarcoma	2	0	1	0	0	4	1	0	1	0	9
Myxosarcoma	3	1	0	1	0	1	0	0	0	1	7
Probable leiomyo or fibrosarcoma											
Round cell	5	0	2	1	4	10	1	1	0	2	29
Spindle cell	3	2	4	1	1	1	1	2	1	2	21
Mixed cell	2	1	0	2	2	1	3	1	0	0	12
Osteogenic sarcoma	1	0	0	0	1	2	3	1	0	1	9
Malignant lymphoma	1	0	0	2	3	1	1	0	0	0	8
Rhabdomyosarcoma	5	1	0	0	0	0	2	0	0	0	8
Sarcoma (? type)	2	0	0	1	3	7	1	2	0	1	17
Other	3	2	2	2	0	2	0	1	0	0	17
Distant metastases											
Lung	2	0	0	0	0	1	3	1	0	0	7
Liver	0	0	0	1	0	1	1	1	0	1	5
Other	0	0	0	3	0	0	3	1	0	2	9

*This table is computed from the cases reported by Alberran ²⁰ ones added by Wilder ²² and those collected from the literature since 1905 and outlined in Tables I and III. Reports by Munves ²¹ and Cecil ³⁹ give many more cases but the various series listed by them probably represent much reduplication. Carcino sarcomata have been omitted.

cellular structure later in life. In producing only local extension and hematogenous metastases this particular tumor, and the other cases reported, have behaved as do the sarcomata. The histologic structure of our tumor, the location of the early lesion in the region of the trigone, and the occurrence of a second embryologic abnormality in the Meckel's diverticulum with heterotopic gastric mucosa, all lead us to feel that the probable origin of this tumor is from mesodermal remnants of the wolffian body. This probably applies to the other reported cases of malignant osteogenic tumors of the bladder as well.

The possibility of our tumor representing a sclerosing tumor of fibroblastic (desmoid) or smooth muscle origin is unlikely in the absence of any intracellular fibrils with the various special stains despite the fact that the tissue was fresh and fixed immediately. The absence of elastic tissue also supports this concept.

BLADDER SARCOMA

Age and Sex. In our series, cases occurred in all decades, but with a much higher incidence in the first decade, and a second peak in the fifth

TABLE III
CASES OF PRIMARY SARCOMA OF THE BLADDER REPORTED SINCE 1905

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1905	Wilder ²⁶	M	48	Hematuria frequency dysuria—1 yr	Trigone on left	Round cell sarcoma	?	Died—6 wks
		M	53	Hematuria frequency dysuria retention—1 yr	Above left ureter	Fibrosarcoma	?	Died—7 wks uremia
		M	62	Hematuria frequency dysuria—6 mos	Left lateral wall	Spindle and round cell sarcoma	?	Excision Living 2 mos Failing rapidly
1907	Whiteside ²³	F	57	Hematuria pain frequency	?	Spindle cell sarcoma	None	Died—2 mos hydro-nephrosis
1908	Sottile ²¹	M	6 mos	Retention	Posterior wall	Sarcoma	?	Died—1 wk
1909	Sicard and Malgouère ²²	F	40	Hematuria dysuria	Diffuse	Sarcoma	None	Died—8 wks pyelo-nephritis
1909	Lecène and Chen ²⁶	M	82	Hematuria retention	Posterior and superior wall	Fibrocellular sarcoma	None	Died—8 days postoperative
1914	Bockenhimer ²⁷	F	40	Hematuria bladder pain cachexia	Posterior and right lateral wall	Sarcoma	None	Excision Cured???
1914	Binney ²⁸	M	74	Frequency	Posterior and left lateral wall	Leiomyosarcoma	None	Died—3 days pyelo-nephritis uremia
1915	Harpster ²⁹	F	55	Hematuria	Trigone over left ureter	Mixed cell sarcoma	?	Died—3 days postoperative
1917	Mixter ³⁰	F	3½	Hematuria retention	Lateral to right ureter	Embryoma	?	Excision Well—2 yrs
1918	Lambrethsen ³¹	M	33	Hematuria dysuria	Superior wall	Round cell sarcoma	Regional lymph nodes	Died—days postoperative
1920	McKenna ²⁹	F	42	Hematuria—6 mos	About left ureter	Spindle cell sarcoma	None	Excis living when reported
1921	Stein ³³	M	55	Abdominal pain on urination	Left bladder roof	Sarcoma	?	Died—4 mos
1923	Loven ³¹	F	20	Urinary retention—10 days	Neck of bladder	Round cell sarcoma	None	Died—1 mo
1924	Leroux and Marion ³⁵	F	44	Hematuria frequency	Multiple nodules	Plasmocytoma	?	Well—1 mo
1925	Jameson ³⁶	M	29	Retention abdominal pain	Diffuse	Spindle cell sarcoma	None	Died—18 days hydro-nephrosis
1925	Smith ³⁷	M	33	Retention abdominal pain	Trigone—right lateral wall	Round Cell sarcoma	Local muscle jejunum kidney	Died—3½ mos
1925	Bottari ³⁸	F	16	Hematuria abdominal mass	Diffuse	Spindle cell carcinoma	?	Died—postoperative renal insufficiency
1926	Cecil ³⁹	M	27	Hematuria renal retention—6 mos	Trigone lateral and posterior walls	Fibroblastic sarcoma	None	Living—1 yr, cystectomy

TABLE III—(Cont.)

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1926	Caulk ⁴⁰	F	71	Hematuria pain in bladder—2 mos	Dome of bladder	Spindle cell sarcoma	?	Died—1 mos, pneumonia
1926	Saturski ⁴¹	F	33	Hematuria frequency, burning, dysuria	Posteriorly left of midline	Fibromyoma	Local recurrence	Living—10 mos
1927	Marogni ⁴²	M	36	Hematuria frequency tenesmus	Posterior at base of dome	Lymphosarcoma	?	Died—postoperative
1927	MacKenzie and Chase ⁴³	F	69	Hematuria abdominal pain	Trigone	Rhabdomyosarcoma	Lymph nodes, liver duodenum	Died—6 mos
1928	Garofalo ⁴⁴	M	51	Hematuria frequency tenesmus	Posterolateral wall	Angiosarcoma	?	?
1928	Weiss and Dreyfus ⁴⁵	M	6 mos	Urinary obstruction ecchyma	Trigone posterior wall	Myosarcoma	Lung	Died—1 mo
1928	Foulds ⁴⁶	M	74	Hematuria, pain, bladder spasm	?	Sarcoma	Local recurrence	Living when reported
1928	Bryan ⁴⁷	M	42	Hematuria, dysuria, tenesmus	Diffuse	Round cell sarcoma	None	Died—postoperative
1929	Hager and Hunt ⁴⁸	F	53	Hematuria—10 days	Posterior wall	Leiomyosarcoma	None	Living—1 yrs cystectomy
1929	McCarthy Stepta and Halperin ⁴⁹	M	48	Hematuria nocturia burning	Posterior to trigone	Spindle cell sarcoma	?	Excision Living—8 mos
		M	4	Frequency pain dysuria—3 mos	Left lateral wall	Spindle cell sarcoma	?	Died—1 mos
1929	Descalopoulos ⁵⁰	?	9 mos	Urinary obstruction abdominal mass	Anterior wall	Myoma	Peritoneal	Died—3 mos
1929	Houette ⁵¹	M	13 mos	Frequency	Posterior and superior walls	Rhabdomyoma	?	Died—5 days hydro-nephrosis
1929	MacKenzie and Hawthorne ⁵²	M	54	Hematuria burning—1 wk	Roof extending down to bladder neck	Round cell sarcoma	?	Excision and radiation Living—10 mos
1930	Smith ⁵³	M	48	Hematuria nocturia kidney pain weight loss	Left lateral wall	Spindle cell sarcoma	Local invasion	Died—6 wks
1930	Caylor and Walters ⁵⁴	M	4	Hematuria frequency, dysuria—8 mos	Superior and antero-lateral walls	Leiomyosarcoma	?	Died—3 mos
1931	Mintz ⁵⁵	M	5	Hematuria frequency dysuria abdominal pain—4 mos	Posterior inferior wall	Leiomyosarcoma	None	Died—1 yr
1931	Dupont and Misrahi ⁵⁶	F	32	Hematuria frequency weight loss	Trigone and right lateral wall	Reticulolymphosarcoma	?	Excision Living when reported

TABLE III—(Cont.)

Date	Author	Sex	Age	Symptoms	Location	Diagnosis	Metastases	Course
1932	Lazrus and Rosenthal ⁶⁷	M	2	Hematuria frequency tenesmus—4 wks	Diffuse	Myosarcoma	None	Died—11 mos
1932	Eljasz ⁶⁸	M	16	Hematuria	Left lateral wall	Kaposi	?	Living
1932	Krauskopf ⁶⁹	F	60	Frequency pain abdominal mass	Diffuse	Leiomyosarcoma	?	Died—36 days anuria
1932	Garvey and Barry ⁶⁰	F	13	Hematuria frequency dysuria—4 wks	Trigone and base	Spindle cell sarcoma	Local extension	Died—7 mos
1932	Weiss and Meyer ⁶¹	?	4½ mos	Frequency, dysuria—1 mo	?	Myosarcoma	?	Died—1 wk, uremia
1932	Gazzolo ⁶²	M	61	Hematuria frequency dysuria	Trigone	Fusocellular sarcoma	?	Living when reported
1933	Czaykowski ⁶³	M	34	Hematuria frequency—2 yrs	Left upper wall	Polymorphofusocellular sarcoma	?	Excision Living—3 mos
1933	Krauskopf ⁶⁴	M	74	Hematuria, frequency weight loss—5 wks	Right lateral wall	Leiomyosarcoma	None	Died—5 mos
1934	Harvey and Tennant ⁶⁵	F	1 mo	Cachexia pelvic mass	Trigone	Neurogenic sarcoma	None	Died—18 hrs
1935	Jelm ⁶⁶	M	47	Hematuria frequency, dysuria—2 mos	Right posterior wall	Mixed cell sarcoma	?	Died—6 wks
1935	Diaz Munoz ⁶⁷	M	63	Hematuria dysuria, frequency—18 mos	Diffuse	Polymorphocellular sarcoma	?	Died—days postoperative
1935	Kitagawa ⁶⁸	F	58	Hematuria frequency—6 mos	Posterior wall	Round cell sarcoma	None	Died—7 mos
1936	Welford Hill and Hillebrand ⁶⁹	?	?	Hematuria incontinence pain—5 mos	Base	Rhabdomyosarcoma	?	Died—6 mos
1937	White and Gurnes ⁷⁰	M	2	Frequency incontinence, straining—8 mos	Anterior wall	Rhabdomyosarcoma	?	Died—weeks
1937	Feggetter ⁷¹	M	38	Hematuria dysuria frequency, renal pain	Trigone over right ureter	Spindle cell sarcoma	?	Living but failing rapidly
1937	Feggetter ⁷¹	F	10	Hematuria—1 day	Fundus	Sarcoma	?	Excision Living—1 yr
1937	Weyerbacher and Balch ⁷²	M	4	Hematuria frequency, retention, pain—1 wk	Left lateral wall	Leiomyosarcoma	Lungs	Died—3 wks
1938	Pieh and Weber ⁷³	F	80	Hematuria frequency	Trigone	Spindle cell sarcoma	None	Died—2 days postoperative
1938	Ashburn and Wollenwaber ⁷⁴	M	59	Pain in bladder, nocturia burning	Left lateral wall	Leiomyosarcoma	None	Died
1938	Registry ⁷⁵	M	72	Hematuria	Right lateral and posterior wall	Spindle cell sarcoma	?	Died—days postoperative
1938	Craver ⁷⁶	F	33	Hematuria	Superior wall	Leiomyosarcoma	?	?

OSTEOGENIC SARCOMA OF BLADDER

TABLE III—(Cont.)
Location
Diffuse

Date Author

1938 Hirsell and Brown⁷⁷

Sex Age

Symptoms
Hematuria frequency,
dysuria—3 mos

1939 Uhlmann Grossman
and Calbin⁸⁰

Sex Age

Symptoms
Hematuria bladder pain—
1 wk

1939 Kretschmer and
Doerling⁸¹

Sex Age

Symptoms
Pain on urination

1939 Ratliff and Valk⁸²

Sex Age

Symptoms
Hematuria frequency,
dysuria weight loss

Sex Age

Symptoms
Hematuria frequency,
incontinence

Sex Age

Symptoms
Dysuria frequency,
straining—6 mos

1939 Vermooten⁸³

Sex Age

Symptoms
Frequency, straining—
9 wks

1939 Munger⁸⁴

Sex Age

Symptoms
Hematuria frequency
difficulty in urination

1940 Gaye⁸⁵

Sex Age

Symptoms
Hematuria frequency
weight loss—5 wks

Sex Age

Symptoms
Cystitis

1940 Octama⁸⁶

Sex Age

Symptoms
Hematuria frequency

1941 Mingazzini⁸⁷

Sex Age

Symptoms
Dysuria frequency
abdominal swelling

1941 Keane⁸⁸

Sex Age

Symptoms
Hematuria frequency

1941 Bugbee and Dargeon⁸⁹

Sex Age

Symptoms
Hematuria dysuria—3 wks

1941 Bonne⁹⁰

Sex Age

Symptoms
Hematuria frequency
pain retention

1942 Kretzman⁹¹

Sex Age

Symptoms
Hematuria frequency
cystitis—25 yrs

NOTE: Reports of cases recorded by Watkins⁹² Montenegro⁹³ Tisso⁹⁴, Martelli⁹⁵, Okubo⁹⁶ Astraldi and Monserat⁹⁷ Bongiorno⁹⁸ Wagner⁹⁹ and Price¹⁰⁰ were not avail-

Diagnosis
Myoblastic sarcoma

Leiomyosarcoma
Fibrosarcoma

Round cell sarcoma

Rhabdomyosarcoma

Leiomyosarcoma

Rhabdomyosarcoma

Rhabdomyosarcoma

Myxofibrosarcoma

Rhabdomyosarcoma

Leiomyosarcoma

Leiomyosarcoma

Leiomyosarcoma

Polymorphiocellular
sarcoma

Mixed cell sarcoma

Leiomyosarcoma

Sarcoma

Myxofibrosarcoma

Lymphosarcoma

None

Metastases,
Lymph
nodes, lung
liver and bone
?

Mesentery
colon
?

Local
extension
None

None

Local
extension
None

Local
extension
None

Local
extension
None

Local
extension
None

Liver
intestine
None

None

None

?

?

Excision
X-ray
mos

Died—3 mos

Died pyelonephritis

Excision
X-ray
20 mos

Living—

decade. The proportion of male to female cases is about 2:1, and this agrees with the statistics previously assembled by Cecil.³⁹

Pathology Grossly, the tumor may be either localized or diffuse. The vast majority of the localized tumors occurred in or about the trigone, frequently developing near one of the ureteral orifices. The diffuse growths also often involved the trigone and those tumors reported in Table II as being located elsewhere usually involved this structure as well. Many of the tumors have been polypoid or pedunculated, or started out in that form as did our case.

The histologic variants are indicated in Table II. The great bulk of the tumors are either leiomyosarcomata or fibrosarcomata, particularly if one includes the round, spindle and mixed cell types in this group. We believe they should be so considered. The most unusual cases reported have been the plasmocytoma recorded by Leroux,⁴⁵ an angiosarcoma reported by Garofalo⁴⁴ and a case of multiple hemorrhagic sarcoma of Kaposi, published by Eljasz.⁵⁸ The carcinosarcomata have been purposely omitted because of the unsettled question as to the actual nature of their cellular components.

Diagnosis The clinical aspects of the various sarcomata do not offer any differential points from the carcinomata of the bladder. Hematuria is an almost constant symptom (Table II), and it may be constant or intermittent, massive or slight. Dysuria, frequently with severe pain and frequency, are the next most frequent symptoms. Since the tumors grow rapidly, urinary obstruction develops early, so that varying degrees of frequency, incontinence and retention follow. Occasionally tissue fragments are passed in the urine and recognized.

The clinical diagnosis is simply that of bladder tumor, the diagnosis of sarcoma being entirely a histologic one.

Course The tumors grow rapidly and infiltrate locally, so that the majority of the cases die in less than six months. It is interesting that so few of the cases have shown blood stream metastases, the more usual extension being through the bladder and neighboring tissues. Involvement of one or both ureters is almost constant, so that hydronephrosis, pyelonephritis and nitrogenous retention usually occur and are frequently the immediate cause of death along with cachexia.

Therapy has been attempted by both complete cystectomy and radium and roentgenotherapy. Several cases have survived for one year, as shown by the reports assembled in Table III, but to date no five-year cures have been reported. Since metastases occur by local extension and infrequently by the blood stream, complete cystectomy, as suggested by Cecil,³⁹ should be attempted wherever possible.

SUMMARY

1. A case of primary osteogenic sarcoma of the bladder containing large amounts of alkaline phosphatase histologically and showing a range of phosphatase activity identical with that of primary osteogenic sarcomata of bone is recorded.

2 The possible origin of osteogenic tumors of the bladder from urinary epithelium (metaplasia) and embryologic rests (wolffian body) is discussed

3 A high alkaline phosphatase content in a tumor by chemical and histochemical methods while characteristic of osteogenic sarcomata should not be regarded as diagnostic until we have further knowledge of the phosphatase activity of tumors derived from cells normally rich in phosphatase, as those of bladder mucosa and kidney

4 The literature of sarcoma of the bladder has been reviewed and the characteristics of the various sarcomata of the bladder outlined

5 Sarcoma of the bladder occurs in all age-groups, but with peaks in early and later life Histologically, the tumors are most frequently fibrosarcomata or leiomyosarcomata or variants of these

6 The diagnosis of sarcoma of the bladder is entirely a histologic one

7 At present radical and complete cystectomy offers the only chance of a cure

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MENINGIOMA

CASE REPORT

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To REPORT a single case of so common a lesion as a meningioma would be unjustifiable were it not that I believe the tumor in question to be the largest intracranial neoplasm ever reported. Removal of the mass was successfully carried out and recovery was uneventful. In addition, the case illustrates the preponderance of symptoms referable to structures in the posterior fossa which may sometimes accompany a mass on the superior surface of the tentorium cerebelli.

Case Report—V U Hosp No 116805 J L O, white, male, age 25, was referred by Dr F H Booher, of Lynchburg, Tenn, September 16, 1941, because of headaches and failing vision.

For many years he had suffered from repeated attacks of bronchial asthma, sometimes requiring epinephrine for relief. Three years before admission, he was jaundiced for a few days. There had been no other significant illnesses or injuries. One grandmother had suffered from mental disease of unknown nature.

Fifteen months prior to admission he began to have bitemporal or generalized headaches of slowly increasing frequency and duration. Three months later, the headaches were sometimes associated with vertigo and occasional vomiting, and he began to be unsteady in walking. For eight months, he had noted progressive loss of hearing in the right ear without tinnitus, some impairment of his sense of taste ("sweet things taste bitter") intermittent difficulty in swallowing, and occasional hoarseness. During the two months prior to admission, his vision had failed rapidly in both eyes.

Physical Examination—The patient was alert and cooperative. Memory and speech were normal. His neck was stiff, and his head was held in a retracted position. Vision was limited to perception of moving fingers at two feet. The visual fields could not be determined. The pupils reacted normally. There was marked bilateral papilledema, with advanced secondary optic atrophy. A slow, coarse nystagmus was present on lateral gaze to either side, equal in each direction. The fifth and seventh cranial nerves were unaffected. Hearing tests showed that air conduction was almost nil, and bone conduction greatly reduced on the right. The Weber was referred to the left. The gag reflex was not obtained on either side, but pharyngeal sensation seemed normal. Swallowing, phonation and tongue movements were normal at the time of examination.

Strength was equal on the two sides, and no loss of sensation was found. The reflexes were normal and equal. Babinski's sign was not present. There was no clonus. Coordination was good in the upper extremities but the patient walked with a broad base and was very unsteady. He veered to the right and tended to fall to the right.

There was a pigmented mole over the sternum, and a small, firm, subcutaneous nodule, possibly a neurofibroma, just below the left clavicle.

Laboratory observations were noncontributory. Roentgenograms showed marked thinning of the entire skull with greatly increased "convolutional" markings. In the region of the lambdoidal suture on the right was an area of thickening, suggestive of hyperostosis, but there was no surrounding increase in vascularity. All sutures

were markedly separated. The sella turcica was larger than normal and the dorsum sellae was eroded. There was moderate erosion of the petrous ridge on the right.

The tentative preoperative diagnosis was right acoustic tumor, but because of atypical features ventricular estimation and, subsequently, ventriculography were carried out. Ventriculograms showed the right ventricle displaced anteriorly and flattened on its posterior aspect, evidently by a right occipital mass (Fig. 1). Removal of the lesion was undertaken immediately.

Operation—September 25, 1941. Under intratracheal ether anesthesia, a large osteoplastic flap was turned down in the right occipital region, extending to the lateral sinus posteriorly and almost to the longitudinal sinus medially. The bone was exceedingly



FIG. 1.—Ventriculogram showing the anterior displacement and posterior compression of the right ventricle by the enormous tumor in the right occipital region.

thin (indeed, in several spots, its entire thickness was eroded) except in the thickened area seen in the roentgenograms. This area was slightly adherent to the dura, but was easily separated. When the flap was reflected the adherent area of dura was seen to show the characteristic radial "puckering" indicating an underlying meningioma.

A circular incision was made in the dura to include the adherent area and the remainder of the dual flap was reflected separately, leaving this area attached to the enormous tumor which was thus brought into view. An area of tumor-surface about five centimeters in diameter was exposed. Numerous large vessels connected it with the surrounding cortex laterally and anteriorly. Gentle dissection posteriorly and medially showed no invasion of, or direct attachment to, the great dural sinuses. The superficial vascular connections were coagulated or clipped and divided, and the dissection of the cortex from the surface of the tumor begun. It became apparent immediately, however, that the mass extended so far beneath the brain that it could not be removed intact without irreparable damage. Accordingly with the electro-surgical loop, a large intracapsular excavation was produced. This greatly reduced the size of the lesion and allowed partial collapse of its walls. It was then possible gradually to enucleate the remaining mass intact. Deeper vascular attachments were troublesome, but were secured without excessive difficulty. The central defect in the dura was left open, the wound closed, and the patient given a transfusion.

Postoperative Course—Recovery was uneventful except for some temporary accu-

mulation of cerebrospinal fluid (which had escaped through the dural defect) under the scalp. When discharged on the 27th postoperative day, he walked with evidence of weakness, but without staggering.



Fig 2—Two views of tumor and "scallops," removed by the electrocautery loop. A. The presenting surface with excavation. B. The deep surface which lay on the tentorium.

Immediately after operation, he was unable to perceive light, but at discharge he could count fingers at three feet. Four months later, the vision in the right eye was 2/200, and ten months after discharge it was 5/200 in each eye. At the last examination, 20 months after operation, the vision was unchanged, and there was marked secondary optic atrophy. No other symptoms or signs were present.

Pathologic Examination—Gross The tumor (Fig 2) was nearly spherical, with a diameter of 12 cm. Its weight was 374 Gm. The capsule was smooth, thick and intact except at the area of excavation (which had included the dural attachment). The tumor substance was firm, slightly granular in appearance, and apparently perfectly uniform throughout.

Microscopically, the tumor was a typical meningioma of fibroblastic type. The elliptical cells were arranged in parallel streams and whorls and were supported by a fine collagenous network. It was very vascular. Very rare mitotic figures were seen.

Comment—The frequency with which the slowly growing meningiomata attain great size has been discussed in many publications. Cushing and Eisenhardt¹ cite numerous reports of large tumors, the largest of which was the otherwise unpublished 341 Gm meningioma removed by Hoen. The largest in Cushing's series of 313 meningiomata weighed 310 Gm.* Davidoff² removed, in three stages, masses of tissue aggregating 835 Gm, but this included an enormous hyperostosis of the skull.

So far as I am aware, therefore, the meningioma reported herein exceeds in size any primary intracranial tumor previously removed.

As already mentioned, the symptoms in this case were, for the most part, referable to the posterior fossa and were probably attributable to compression and displacement of the cerebellum and brain stem by the huge mass lying on the superior surface of the tentorium.

SUMMARY

The successful removal of a meningioma weighing 374 Gm is reported.

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* At several secondary operations, Cushing removed recurrent masses of tumor exceeding 400 Gm.

ANTERIOR SACRAL MENINGOCELE

REPORT OF THREE CASES

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ANTERIOR SACRAL MENINGOCELE is of sufficient rarity to warrant the report of another case successfully removed surgically. Two other cases, untreated, are included in this report. Collet and Jackson¹ have reviewed the literature and have reported their case, with a description of the operative treatment employed.

In summarizing the article of Collet and Jackson, only 23 cases, including their own, were found in the literature. Their case made a complete recovery after surgical treatment. Of the remaining cases reported in the literature,



FIG 1—Case 1. Roentgenogram showing absence of sternum on left. Air in bowel obscures first and second sacral segments.

18 were treated, with a mortality of 44 per cent. Of these 18, eight were cured, and two remained the same. The first case was described by an anonymous surgeon in 1837. The ratio of occurrence was of 203 females to males. Most of the cases occurred in the second and third decades of life, and commonly were found as complications of menstrual disturbances and of pregnancy. Attempts to open the tumor through the vagina met with death from meningitis (Kronei, in 1881, and Thomas, in 1885). The first successful operative approach was in 1903, by Pupovac, who employed a dorsal incision, exposed the tumor, resected part of its wall, and closed the remainder of the sac upon itself with sutures. Grossman, in 1906,

exposed the pedicle of the tumor through a posterior incision and sutured it to the periosteum of the sacrum. Coqui, in 1916, and Roux, in 1918, both exposed the pedicle of the sac at celiotomy and ligated it, with resultant cure. In 1929, Drennan employed the posterior approach unsuccessfully. In 1938, Santy, through a posterior approach, removed the meningocele and



FIG. 2—Case 2. Roentgenogram showing markedly deformed sacrum and lower lumbar vertebrae.

two dermoids. A cerebrospinal fluid fistula drained for six months, but the patient made a good recovery.

In the case reported by Collier and Jackson a retroperitoneal tumor of other origin was suspected preoperatively. The tumor was first approached through the abdomen, but because the exposure was inadequate, the patient was placed in the prone position, and through a posterior incision just lateral to the midline the tumor was exposed and the pedicle ligated with silk. The sac was left intact after it had been aspirated. No nerves were found within the sac. A small pack was left against the ligated pedicle and brought out through the wound. Postoperatively, the hips were kept elevated above the level of the shoulders for six days, and the foot of the bed elevated for about 13 days. The wound healed in 41 days.

Of the three cases herein reported, only one complete history and operative procedure is available (Case 3). Cases 1 and 2 did not come to surgery and are reported through the courtesy of Dr. Don King.

CASE REPORTS

Case 1—G. McW., white female, age 50, married, entered the hospital in March, 1940 with the complaint of pain in the back and shortness of breath. For several years before entry she had been followed with no particular complaint except for occasional pains in both legs. Frequent examinations during this period were unrevealing. Three months before entry she had had pneumonia. There was no history of rheumatic fever. She had borne children without difficulty.

Physical Examination—Temperature was 38.2°C , pulse 140, respirations 30. Blood pressure 160/60. She was pale and her back could hardly be touched because



FIG. 3.—Case 3. Anteroposterior and lateral roentgenograms showing marked defect of left portion of sacrum.

of severe pain. Positive physical findings included rales over both lung fields, posteriorly. A diastolic murmur was heard along the left sternal border and at the aortic and pulmonic areas. A large, smooth tumor was palpable in the left pelvis, on rectal examination. A roentgenogram of the sacrum showed a complete absence of the sacrum on the left (Fig. 1). Successive blood cultures showed 50 to 200 colonies of hemolytic streptococci. Numerous other laboratory studies were made in relation to her septicemia.

Thinking that the pelvic mass might be an abscess, she was operated upon for incision and drainage. The tumor was approached through the left buttock, but when it was seen that the subcutaneous tissues were not edematous, aspiration through the incision yielded no pus. The wound was closed. Aspiration was then done through the sacral defect, and cerebrospinal fluid was obtained. The pelvic mass disappeared following the aspiration.

Her blood cultures remained consistently positive until a few days before death, in spite of chemotherapy and transfusions. Her temperature varied between 38°C and 39.5°C . She died 18 days after admission to the hospital.

Case 2—T. T., white, male, age 29, entered the Bone and Joint Service in

October, 1940, for correction of a chronic ulceration of the skin over the cuboid bone of his right foot

He had been born with a soft tumor over his sacrum, but without other noticeable deformity. He was normal throughout infancy until the age of four when he had a serious prolonged illness, diagnosed as "cholera morbus," characterized by severe diarrhea and high fever. After this illness, he had difficulty in walking. It was noted that he had a "stamping" gait with the left foot, and that the right ankle turned completely over so that he walked on the lateral side of the foot. During the course of the illness, urinary incontinence developed which persisted until he was 14 years old. Since that age, he had regained control of his urination, but had had frequency. Urethral dilatation a year before entry markedly improved his frequency. Since the boyhood illness he had had numerous pressure sores over his ischiae and over the lateral side of his right foot.

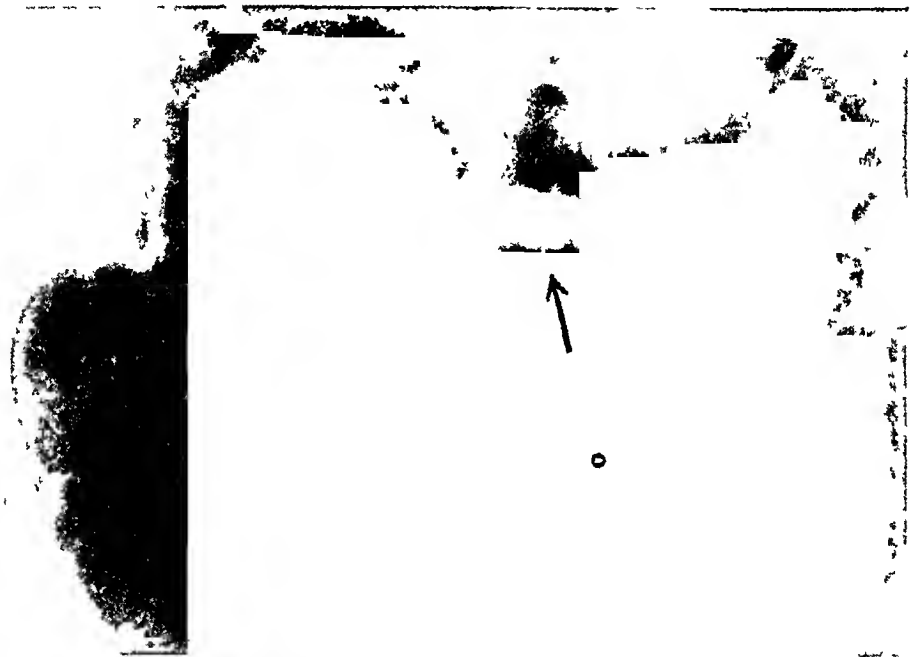


FIG 4.—Case 3. Spot fluoroscopic film, Anteroposterior view of lumbosacral region just after lipiodol injection. Lipiodol outlines caudal portion of subarachnoid space, but does not enter meningocele.

Physical Examination—Anal sphincter tone was present, but thought to be diminished. There was a soft semifluctuant mass, about 10 cm in diameter, over the left side of the buttocks, overlying a palpable defect in the left side of the sacrum. The mass was also felt rectally. Pressure over the mass produced a headache. The right leg was in marked equinovarus, with weight-bearing upon the cuboid bone. The right foot was in marked calcaneocavus position. Hypesthesia was present only over the feet and perineum.

A roentgenogram showed malformation of the entire sacrum (Fig 2). Osteomyelitis of the right cuboid bone of the foot was also noted. Aspiration of the sacral mass was not attempted. Since he had no symptoms referable to his meningocele, no surgical treatment was advised. His right leg was amputated below the knee. He made a good recovery from this operation.

It should be noted that the meningocele was palpable posteriorly as well as rectally in Case 2. The osseous anomaly involved the entire sacrum and lower lumbar vertebrae in this case.

Case 3—H. E., white, female, age 29, unmarried, entered the hospital in September,

1942, complaining of lifelong constipation. She sought medical advice when laxatives no longer had effect. She had no other symptoms of rectal disease. She had always been healthy, otherwise. Her menarche was at 11 years. Menstrual periods were regular every 28-30 days, lasting 5-6 days with severe dysmenorrhea during the first two days of the period.

Physical Examination—No tumor was palpable abdominally. Pelvirectal examination revealed a huge mass which completely filled the left pelvis, crossing the midline. The rectal mucosa was freely movable over it and the mass was slightly compressible. The rectum was displaced to the right. The uterus was anterior and small. There were no adnexal masses or tenderness.

Roentgenograms of the lower lumbar spine and pelvis showed a congenital absence of the left portion of the sacrum (Fig. 3). There were also anomalies of the 4th and 5th lumbar vertebrae. The radiologists detected the pelvic mass and suggested that it might be meningocele. The mass was further outlined with a barium enema which showed the rectum to be displaced to the right and upwards.

A lumbar puncture needle was inserted into the mass just to the left of the palpable bony sacrum. About 200 cc. of cerebrospinal fluid was obtained without discomfort



Fig. 5—Anteroposterior and lateral views of pelvis, two weeks after introduction of lipiodol into subarachnoid space. All of lipiodol is in the meningocele. A few particles of lipiodol remain in spinal canal.

to the patient. The mass disappeared after aspiration. The following day a lumbar puncture was done without difficulty, and 1 cc. of lipiodol was introduced into the subarachnoid space. Fluoroscopic examination showed the lower portion of the dural sac to be flattened as though pushed upon by a mass (Fig. 4). None of the lipiodol was seen to enter the mass or leave the spinal canal (Fig. 4). Fluoroscopic examination was done the following day, and the lipiodol still remained in the spinal canal. Two weeks later, all of the lipiodol was in the pelvic mass (Fig. 5). The diagnosis of anterior meningocele was thus confirmed. All of these procedures were accomplished in the Out-patient Department, with no discomfort to the patient except for low back pain while the lipiodol remained in the spinal canal.

About a month later the meningocele was approached through a posterior incision beginning over the 4th lumbar vertebra and carried down over the sacrum. After division of the fascia over the defect in the sacrum, a tumor, about 14 cm. in diameter, presented itself. The patient's head and spine were lowered beneath the level of her hips. The sac was opened. No nerve elements were seen within it. The empty sac was then

completely dissected free of the pelvic viscera. At its caudal portion, two nodular structures were encountered which were thought to be coccygeal glands. These were cauterized with 95 per cent alcohol. The neck of the sac was small and the actual openings into the spinal canal was two and less than one millimeter in diameter. After amputation of the sac, the openings into the spinal canal were closed with mattress sutures of silk. The head of the table was elevated above the level of the hips. No fluid was seen to emerge from the suture line. The dead space was filled with normal saline, and the wound was closed with double medium silk sutures. The wound was dressed without pressure. A transfusion of 500 cc of citrated blood was administered during the procedure.

Postoperatively, she was given a low-residue diet. The foot of the bed was elevated for about ten days. On the 10th postoperative day she developed infection in the dead space. This was drained through the wound. Her temperature gradually subsided to normal. She was dismissed on her 18th postoperative day. She had no signs of meningeal irritation at any time. Her wound had healed by the 31st day, and she had returned to work on the 33rd day after operation. Six months after operation, she felt well, was normally active, and had little trouble with constipation.

SUMMARY

1 Anterior sacral meningocele is a rare congenital anomaly associated with congenital absence of half of the sacrum.

2 Symptoms due to anterior sacral meningocele are those produced by pressure of the tumor upon pelvic viscera, or displacement of the latter by the tumor.

3 Until recent years, operative treatment of anterior sacral meningocele has been attended by high mortality from meningitis.

4 Successful removal of an anterior sacral meningocele is achieved through a posterior approach.

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BOOK REVIEW

ENDOSCOPIC PROSTATIC SURGERY By Roger W Baines, M D St Louis C V Mosby Co, 1943

The terms employed in urologic surgery seem to be constantly undergoing change. Though it is barely thirty years since the operation with which this monograph is concerned was first introduced, it seems always to be assuming new titles. We have heard it called "transurethral," "interurethral," "intra-urethral," or "*per methram*." Again, it is "intervention upon the prostate by the endoscopic route," or perhaps "endoscopic excision." The title Dr Baines has chosen is perhaps, as good as any—if not better than most—and it is to be hoped may prove sufficiently authoritative to provide a permanent standard term designating this particular procedure.

The historical section is unimportant and might be passed over were it not that it seems necessary to remark that the selection of *what was to be left out* might have been made with more wisdom and accuracy. The "Foreword," likewise, fails to give credit to several of the chief pioneers whose work contributed so much to the present high standing of the operation, both as to mechanical equipment and operative technic. It was the men who never let their enthusiasm run away with their reasoned judgment, who were able to evaluate, truly, the proper place of endoscopic resection, so as to make use of it *only* when all the circumstances combined to make that use logical, or even inevitable, who really brought the procedure to general acceptance.

There is no doubt, in the reviewer's mind, that prostatic resection has come to stay, and is in no wise a fad of the extremists. But not until *all* urologic surgeons realize that it is applicable only in carefully selected cases, and should never be undertaken routinely, whether or not the patient would be better served by some other type of intervention, that it will come to full usefulness. The technic selected should be that best suited to the pathologic findings in any given case, and not the operation the surgeon is most skilful in performing. To perform the endoscopic procedure properly requires exactly as much study and practice as is necessary for the suprapubic or perineal routes, as Dr Baines most properly emphasizes, and no man is a competent surgeon unless he can perform all three with equal precision and success.

Along the Eastern seaboard the proportion of excisions *per methram* to the two other types of procedure seems better balanced than in the farther West. Our western colleagues seem to be still sharply divided—one faction being extremely conservatives, while the other proclaims, on all occasions, that large numbers—if not hundreds—of endoscopic resections have been performed upon patients of all ages, with prostates in all stages of hypertrophy, with almost 100 per cent perfect results, and fewer deaths than follow the older procedures.

Dr Baines, however, joins neither faction. He feels that a levelling-off process has been for some time at work and that the indications for the use of the endoscopic route can be set up definitely by a rule far more accurate than that of thumb. The number of "recurrences" presented in the larger medical centers for reoperation, attest, only too eloquently, how often the method is unwisely employed, and by those who have not acquired sufficient skill to perform it properly, even when the indications point unerringly to the employment of the endoscopic route.

The chapter on anatomy and pathology is clear and concise, the section on the prostatic blood supply being especially well illustrated and described. Appropriate emphasis is laid on the likelihood and dangers of hemorrhage. The whole area is often so hemorhagic that it is impossible to pick out the individual bleeding vessels and cauterize them separately. If a "mass" cauterization is given to all the tissue cut, deep sloughing is almost sure to result, so that the necrosis is as extensive and dangerous as in other technics, which have been criticized on that account.

Most excellent is the chapter on electric current modifiers. It might well be thoughtfully read by every urologist who takes up this type of practice. Because at least 50 per cent of his success depends upon his mechanical equipment, the most finished operator will be helpless if his machine fails.

Of the portion of the book dealing with punch instruments, the reviewer does not feel qualified to speak because he is unfamiliar with this equipment. This is due to the fact that he has found instruments of the McCarthy type, with the fore-oblique lens system afford clear visualization at all times, making the "blind" maneuvering with this type of punch a most unsatisfactory procedure. Dr Barnes' description of his technic is brief, clear, and to the point, and his consideration of possible emergencies, good. There has never yet been an operator so skilful or *lucky* that he has not been faced with some of the accidents here enumerated. Injury to the external sphincter is perhaps the worst that may befall—from the patient's viewpoint at least—and the precautions mentioned should be scrupulously observed. The book offers many valuable suggestions.

THOMAS J. KIRWIN

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PLANNED TIMING IN THE TREATMENT OF WOUNDS AND INFECTIONS BY MEANS OF INFREQUENT OCCLUSIVE DRESSINGS

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THIS PAPER IS an attempt to show how well known surgical principles can be coordinated and most successfully applied by organized, timed technique. The principles to which we allude, and which we believe are soundly based, are widely practiced in the treatment of wounds and infection. They include

1 Efficient first aid by adequate occlusive dressing, relief of pain, hemostasis and temporary splinting^{7, 12}

2 Excision or débridement of fresh wounds as advocated by Depage¹⁰ and by Pierre Duval¹³ during the first phase of the War of 1914-1918, but which had been enunciated by Desault¹¹ in 1813

3 (a) Surgical antisepsis or its more recent descendant, bacteriostasis, as first practiced by Lister,¹ but whose roots are much older

(b) Surgical asepsis as first advocated by von Bergmann⁵ in 1888

4 Wound (curtain) drainage by the employment of packing gauze impregnated with liquid paraffin, as first urged by Rutherford Morison³³ and subsequently by Guild,¹⁹ McKim,²² and by Orr³⁹

5 Closed or occlusive dressings. Most of the emphasis of this principle has recently been placed on "closed plaster technique." This is fortunate for the principle was known to the Egyptians (Smith papyrus) and to Hippocrates who used various immobilizing materials and hardening bandages long before plaster of paris was known, *e g*, bandages impregnated with albuminous material. Primitive peoples have used clay or mud, and this method was used successfully by the Ethiopians during their recent struggle with the Italians. In 1853, Gamgee¹⁶ described the continued fixation of a dressing by starch bandages. Plaster of paris appears to have first been used by Ollier,³⁸ in 1872, to enclose wound and whole limb completely

6 Rest of the part, a principle immortalized by Hilton,²⁷ in 1863

7 Infrequent change of dressings with proper drainage was advocated and practiced by Rutherford Morison,³² in 1881

It will thus be seen that the general principles of closed and infrequent dressings are mainly ancient, and their modern adaption almost one hundred years old

During the first phase of the present world struggle, the War of 1914-1918, considerable impetus was given to the technique of W H Ogilvie,³⁵ by Morison,³³ and by Hey Groves¹⁸ These advocates were strongly supported, subsequently by Gurd,¹⁹ and McKim²² of this hospital, by Orr,^{39, 40} and by Baer,⁴ all of whom studied the problems first hand in the last war

In the recent Spanish War, Trueta^{50, 51} continued the story, and his work has since taken him to Britain where it is still going on It is interesting to note that Ogilvie³⁶ continues to show great interest in this work

The material and experience upon which this paper is based has been taken from the Surgical Wards of The Montreal General Hospital where interest in the technique advocated herein has never flagged Many hundreds of cases of all kinds have been so treated since 1919, including all varieties of fresh trauma, burns and infections of all kinds both aerobic and anaerobic

COMMENTARY ON THE BACTERIOLOGY OF WOUNDS

Apart from the specific relationships of antibacterial measures to particular microorganisms, it is essential to interpret the results of surgical procedures in terms of the bacteria involved Especially have the current problems of chemotherapy, and a better understanding of the physiology of both the tissues and bacteria, stimulated an increasing degree of cooperation between the surgeon and the laboratory

Organisms Found in Wounds—It scarcely needs be noted that the bacteria in wounds are introduced either at the time of wounding, or during subsequent dressings or examinations The varieties of organisms present will depend on the site and degree of wounding, the opportunity for contamination, and the conditions of treatment All wounds and operations become contaminated After all, the best operating conditions yet devised do not approximate the perfection of technique required to handle materials in a bacteriological fashion Infection, however, does not necessarily follow, even when the contaminants are demonstrably pathogenic The living tissues are not inert culture media.

In general, civilian wounds, even when caused by enemy action in the form of air raids, become infected less frequently than do war wounds of a similar nature suffered in combat This is due in part to the more prompt attention to the civilian casualty than is often possible in the field, and to the fact that materials driven into a civilian wound, whether they be street dirt, clothing or skin, are likely to be bacteriologically cleaner than is the case with military casualties

During 1914-18, cases arriving in England shortly after having been

wounded on the highly cultivated soil of France showed a primary infection largely made up of fecal bacteria. Wounds in this stage practically always yielded cultures containing *Cl welchii* and other anaerobic spore-bearers, *B proteus*, and streptococci which were generally of the fecal type. In civilian injuries, either industrial or an raid, anaerobic bacteria are not so common, but pyogenic cocci, the source of which is almost exclusively the human nasopharynx and skin, are found with fair frequency. In addition to these highly invasive bacteria, a wide variety of microbes common to soil, water and air-borne dust may gain access to a wound. These include micrococci, nonhemolytic streptococci, *B coli*, diphtheroids, *B proteus* and *B pyocyaneus*. The status of the latter three has been much discussed, and a note about them may not be amiss.

Diphtheroid bacilli are frequently found in wounds. They are common on the human skin and in dust. They have always been regarded lightly, since they are never found alone and their direct pathogenicity is slight. It is a matter of interest that many of them are inhibited by a factor present in human serum, and the inhibition can be removed by the presence of staphylococci. This may explain why they are not found alone. The symbiotic influence is bilateral, for it was shown long ago that they assist some of the pathogens to grow, and their presence in an infected wound may, therefore, be of some importance.

B proteus and *B pyocyaneus* are usually acquired, if at all, during hospitalization. They pass readily from case to case. *B proteus* usually disappears when wounds are well drained, and persists if sloughs or sequestra are present. Wounds with *B proteus* present have no distinctive character, though granulation may have a somewhat unhealthy appearance, and newly formed epithelium tends to break down. *B pyocyaneus*, the organism of blue pus, is often without obvious significance, though sometimes it seems responsible for systemic symptoms and cessation of healing. Trueta has suggested that the organism may have a beneficial effect on wounds and that it may inhibit the growth of pyogenic staphylococci and streptococci. This has not been confirmed. Both these organisms add much to the foul odor of exudates.

The Subsequent History of the Wound—Before the bacteria begin to multiply there is a latent period usually of two or three hours. This lag may, however, extend to several days if the wound has been thoroughly cleaned and débrided. During this time débridement may remove the contaminants completely. By cultivation of the excised tissue, and subsequently of the plaster-treated wound, Orr-Ewing found that some species present in the excised tissue never reappeared. Even though pathogens may exist in a wound throughout the time of healing they do not always cause manifest disease. This must be remembered in view of the tendency to make bacteriological diagnoses of gas bacillus infection, for example, in the absence of clinical signs.

During the stage of bacterial growth, local infection of the tissue takes

place This infection may remain localized or may spread in a manner determined in large measure by the species of organism

Throughout the course of healing, the danger of secondary infection is ever-present The prevention of this by the infrequent occlusive dressing is one of its major contributions The most serious of the secondary invaders are the pyogenic streptococcus or staphylococcus Both cocci may be found contaminating cases treated by the open or even the closed plaster method, and tend to persist until final healing takes place (though, under pressure dressings, usually without significance) The duration of hospitalization prior to the first discovery of these organisms in a wound shows them to be largely gained subsequent to the time of the initial injury In this respect Hare urges minimal first-aid treatment as a means of avoiding unnecessary exposure of a wound to these human parasites until such time as proper surgical precautions can be observed

During World War I *Streptococcus pyogenes* was present in practically every septic wound, and was responsible for nearly every complication, the commonest of which were cellulitis or erysipelas, formation and persistence of sinuses, and severe constitutional symptoms This organism is feared because of its great invasiveness Occasionally local implantation may pass through lymphangitis to septicemia within 12 hours This ready permeation of tissue spaces and lymphatics is associated with the production by the organism of a fibrinolysin, and the limitation of the extension appears to depend on the leukocytic barrier Before this has formed the damaged tissue is, therefore, extremely vulnerable to the streptococcus, and it is especially important to protect the wound from such contamination before granulation Thereafter such contamination may usually be detected only bacteriologically, but before further surgical intervention cultures should again be made to allow for measures to prevent dissemination of any streptococci present

The susceptibility of the streptococci and the resistance of the staphylococcus to sulfonamides has changed the relative importance of these two organisms in wounds The staphylococcus produces a fibrin coagulum in tissue spaces and lymphatics, and is much more easily localized than is the streptococcus However, as the usual cause of osteomyelitis, and since it does invade the blood stream, the presence of the staphylococcus in wounds is a serious matter

The source of the streptococcus as far as wounds are concerned is the human nasopharynx It rarely survives on the external skin surface, though it may sojourn long enough for the fingers to effect a transfer It may survive on the clothing or bedclothes and may be disseminated with the dust in the air of wards The staphylococcus is found in 50 per cent of human noses, but of greater importance is its frequent presence on the external skin, especially in those addicted to furuncles It is particularly important to realize that such skin carriers cannot be eliminated by scrubbing-up Indeed, one may after scrubbing yield a positive culture where a negative one was given before The need for strict surgical asepsis in

the dressing of wounds is obvious. Other details such as dry sweeping of floors also require supervision.

Gas Gangrene—Gas gangrene is usually a mixed infection. The most important toxigenic species of *Clostridia* are *welchii*, *septicum* and *oedematiens*, while others digest damaged muscle and contribute to improving the opportunities for the chief pathogens. The organisms are carried into the wound at the time of the original injury. Only rarely are they secondary invaders from, for example, unsterile dressings.

Contamination of a wound with these anaerobes does not necessarily result in infection. The spores may germinate and cultures may show persistence of the organisms in a wound, without any clinical manifestations whatsoever, and this probably occurs in a majority of such contaminations. Spooner found two cases of frank infection out of eight air-raid casualties with positive cultures. Furthermore, clostridial infection of the subcutaneous tissues must be recognized as differing sharply in prognosis from the serious condition obtaining when muscle is involved. It is for this latter that the term "gas gangrene" is reserved.

The determining factor in spore germination and bacterial growth is the oxidation-reduction potential of the tissue. Prominent among conditions promoting anaerobiasis are extensive tissue damage, deep narrow puncture wounds, hemorrhage, imperfect drainage, retained foreign bodies, and the presence of other bacteria which may utilize oxygen. Tourniquets and tight packing (coiling) of a wound help to achieve the same purpose. The risk of gas gangrene is commensurate with the degree of infestation of the environment with the responsible organisms. Nevertheless, even in Flanders, during 1914-18, where the heavily fertilized soil must have contaminated well-nigh 100 per cent of the casualties with pathogenic *Clostridia*, the incidence of gas gangrene among the wounded was never, at its highest, greater than about 12 per cent. It is worth noting that wounds sustained by soldiers in a state of exhaustion are followed by a significantly higher incidence of gas gangrene.

Signs of anaerobic infection may appear within a few hours of the injury, or they may be delayed for days. Ninety per cent of infections, however, will reveal themselves within 48 hours. During the early stages the bacteria remain confined to the damaged area, and multiply rapidly. Delay in treatment rapidly accelerates the frequency of gas gangrene. Digestion of the blood and dead tissue yields the characteristic foul exudate, which may permeate along the subcutis and the fascial planes. Injured muscles may be invaded singly or in groups, or a whole segment of a limb may be involved. Histologically, it can be shown that the disease has extended well beyond the point indicated by clinical signs of change. In such areas of apparently healthy muscle, a few fibers can be seen microscopically to have undergone change due to the bacterial toxins. The sarcolemma sheaths of the long individual fibers are easily detached from the supporting connective tissue. This provides a potential space into which edema fluid may readily

pass and carry toxin to cause necrosis of the individual fibers. Such toxin-killed fibers are forthwith invaded by bacteria. The presence of these at any point means production of more toxin and enzymatic hydrolysis of tissue carbohydrates to produce the gas. Either toxins or bacteria may gain the blood stream.

THE RATIONALE OF CLOSED INFREQUENT DRESSINGS

Although much has been written in explanation of the success of the occlusive dressing from both investigative and clinical experience, there is still no general agreement. In all modesty, therefore, it is thought preferable to list briefly our observations and opinions with such comment as may be available from experience.

1 *Rest* This fundamental principal of therapy takes precedence over all other factors. It is, moreover, universally understood and accepted. All the other factors will be found to be subordinate to rest in one way or another (Hilton²⁷).

2 *Prevention or Limitation of Bacterial Contamination* There is ample confirmation of the exclusion of pathogenic bacteria from wounds by occlusive dressings. This is exemplified by the "closed plaster"⁵¹ treatment and by the "pressure dressings"²⁴ as used in burn treatment and plastic surgery. The fact that excessive contamination of wounds by pathogens is the price of frequent change of dressing is, also, well established. In this connection, the work of Hare,²⁵ Trueta and Barnes,⁵² Orr-Ewing, Scott and Gardner⁴¹ is outstanding.

It will, also, be accepted that the saturation of dressings with moist discharges contributed to their penetration by contaminating organisms from bedclothes, anus, etc. Consequently, the thickness and dryness of dressing or plaster are important. To illustrate experimentally, we quote from a personal communication from Neal Owens⁴² "Sections of moistened dressing gauze of different thicknesses are placed on the surface of bacterial cultures in deep petri dishes and their different bacterial diffusion times from bottom to top are estimated. When compared with the rate of diffusion through similar dry gauze pads the rate of diffusion is found to be much more rapid."

3 *Effect on the Local Circulation*—(a) Vascular, (b) Lymphatic
(a) The localizing effect on infection of "pressure dressings" and, in particular, "closed plaster" insofar as the vascular circulation is concerned has been described by Trueta⁵¹ as an active congestion of local tissues under the dressing in many respects simulating the inflammation phenomena. To the authors, the matter seems more easily understood if pressure is regarded as preventing the accumulation of interstitial fluid and, thus, we believe, improving the circulation through the affected part.

(b) The lymphostatic effect of rest alone has been well demonstrated by Field, White and Drinker¹⁵. In addition, it should also, be recalled that bacterial dissemination from an infection takes place *via* the lymphatics at

least preferentially rather than *via* the blood stream Pawlowsky,⁴⁴ 1900, was convinced of this, and Dinker, *et al*,¹⁵ have proven it

4 *Retention within the dressing* of antibacterial and other beneficent products of the body's immunological armamentarium in the exuded serum Very little has been made of this point although its importance may, perhaps, be assumed from the healing in the peritoneal cavity without drainage, or with, at best, only partial drainage, in a diffuse peritonitis In any case, it would appear that body defences operate best either early or late when the involved area is immobilized and contamination prevented by an occlusive dressing

5 *Curtain Drainage*—Whether in fresh trauma or in preinfected cases, the rôle of packing gauze in the wound in providing adequate drainage is generally accepted When paraffin or vaseline is impregnated in the gauze, the usefulness of the drain is increased³² This latter fact has been emphasized by several writers, notably by Gurd and McKim,²³ who described it as "curtain drainage" More recently, in 1941, the rôle of this type of drainage has been urged by Pfeiffer and Smith⁴⁵

6 *Bacteriostasis*—Fundamentally and principally, this phenomenon arises *sui generis* from natural immunologic sources Many attempts have been made, however, to aid the local natural defensive mechanism of the body by chemotherapy BIPP, ZIPP, ZISP, the aniline dyes, particularly acriflavine, and other materials have all been used, and some with considerable success More recently, sulfonamides have been employed in this rôle This local use of sulfonamides has been widely developed, and they have been combined with other bacteriostatic agents and placed in various vehicles At The Montreal General Hospital an oil-in-water emulsion of sulfathiazole was devised in 1941, and has now been used for about two years with gratifying results This emulsion was designed to give both satisfactory curtain drainage and bacteriostasis Previous experience with it has already been described in the literature^{1, 2, 24} A brief review of its rationale and the formula will be found elsewhere in this paper

7 *Adequate Surgical Treatment*—Finally, it should be stated categorically that in compound fractures and in larger wounds, the failure to carry out adequate surgical excision of dead and devitalized tissue, to enlarge the wound, and to relieve fascial tension nullifies all of the foregoing benefits of occlusive infrequent dressings The authors believe that in civil practice as well as under field service conditions, this statement still holds, notwithstanding W H Ogilvie's³⁷ report on the Dunkerque casualties, and the very excellent recent report on the South Sea casualties by Ferguson, *et al*¹⁴ These two reports have indicated that only minimal wound excision or débridement is necessary It is felt by the authors, however, that both of the reports are based upon casualties occurring under special conditions, *ie*, the beaches, sea warfare, or land not long contaminated by dense human or animal population Injuries occurring in more densely populated areas, such as Europe, Asia or America will inevitably be more subject to bacterial contamination and shall demand wound excision

STEP-BY-STEP HOSPITAL PROCEDURE (SEE OPERATIONAL CHART)

A FRESH TRAUMATIC WOUNDS

B PREINFECTED WOUNDS AND SUPPURATING LOCI

A FRESH TRAUMATIC WOUNDS—Predicated upon the knowledge that reasonably safe first-aid measures have been instituted, such as detailed by Cole and Puestow,⁷ and most successful when rapid evacuation is followed by early operation

1 *Emergent*—It must be emphasized at once that antishock and anti-hemorrhage measures take precedence, and that any surgical procedure, especially with anesthesia, must be delayed until these measures are effective. The transfusion of whole blood for the treatment of shock plus hemorrhage, and the administration of oxygen to forestall and combat anoxia are the most important details. Surgical or secondary shock without hemorrhage, as in burns and extensive trauma without hemorrhage, requires only plasma or serum plus oxygen. To carry these measures out adequately, frequent estimations of the red blood cells, hemoglobin, hematocrit and plasma proteins (See Chart)

In exceptional cases the ligation of large blood vessels will necessitate an early examination and dressing change with a temporary plaster encasement. In such instances sulfathiazole emulsion packing is used successfully in the temporarily treated wound. Case No. A-4, illustrates this point.

2 *Sedation* for the surgical procedure requires careful individualization.

3 *Anesthesia*—If a general anesthesia is necessary the inhalation type is indicated. Spinal anesthesia has been shown to offer the greatest risk to acute traumatic cases recovering from shock, hence, it is generally speaking contraindicated. The rôle of intravenous barbiturates should, we believe, be still considered *sub judice*. Reference is made here to the recent report of the Shock Committee of the Canadian National Research Council.³⁴

4 *Removal of First-Aid Dressing*—The emergency dressing should not be removed until the patient is in the operating room. Cultures are taken from the wound at once.

5 *Local Wound Preparation*—This is meticulously carried out with aseptic technique, using gloves and instruments, with swabs of ether, alcohol and iodine, dettol, metaphen or other recognized germicide*. Over the wound itself a sterile gauze dressing is first placed. The skin around the wound is then wiped carefully away from the edges. Copious lavage of the wound with saline or any antiseptic is not favored, although detergents are used when necessary.

6 *Surgical Excision of the Wound (Debridement)* †—(a) Enlargement of the wound is the first step and is essential for adequate exploration. Successful

* The value of pure soap as a germicide as well as a detergent in local wound preparation is stressed by Trueta in his recent publication on the Treatment of War Wounds.⁵³ Haycraft emphasized the same in 1918.²⁶

† For a concise and selective definition of the term debridement the reader is referred to the writings of Desault, Depage and Duval and also Lemaitre.³⁰

excision and extraction of foreign bodies The wound edges are *conservatively* excised at this time The deep fascia is now widely incised, lest eventual tension of tissues favor interference with the blood supply and predispose to gangrene This is a detail of fundamental importance

(b) *Circulation*—Blood vessels are now inspected and all gross hemorrhage arrested Should arterial suture or the use of a vitallium tube⁵⁴ be indicated, it is postponed until the wound excision is completed This applies, also, to suture of nerve, tendon or other structure

(c) *Excision of all Dead and Badly Traumatized* tissue in the depths of the wound This procedure is radical, the whole area of muscle and interstitial tissue being removed, if possible, *en masse* Conservatism has no place here

FIG 1

FIG 2



FIG 1—Operation completed and fracture reduced on Hawley table Enlarged wound partly closed with packing held in place by loose suturing

FIG 2—Gauze dressing saturated with sulfathiazole emulsion covering the wound These figures and four following constitute a pictograph of infrequent protective dressing (closed plaster) of a compound fracture of the tibia

(d) *Amputation*—Should amputation be necessary, the stump is packed open, only sufficient loose suturing of the edges being done to retain the pack (See Case A-4)

7 *Fracture Treatment*—Reduction and fixation of fractures is now done and, where necessary, internal or external fixation carried out

8 *Wound (Contam) Drainage*—From the depths outward, the interstices of the wound are now snugly packed with gauze impregnated with 5% sulfathiazole emulsion* When necessary, the edges of the wound are now loosely sutured (See Fig 1)

* Emulsion sulfathiazole 5% (M G H formula) Sulfathiazole 5%, triethanolamine 2%, distilled water 24%, white beeswax 5%, liquid paraffin 64% The emulsion is used liberally and in excess rather than conservatively Alternatively, B I P P-paraffin gauze technique may be done†

Although not always carried out by the author, this packing may be preceded by the installation of a 5-10% suspension of sulfathiazole crystals or microcrystals This is carried out in such a manner as to leave a frosting of the crystals in the depths and on the surface of the wound, after all excess suspension has been spilled or mopped up

FIG 3



FIG 4

FIG 3 ---Large pad of mechanic's waste covering whole leg and wrapped in a towel or gauze bandage
 FIG 4 ---Additional padding with sheet wadding from toes to mid thigh

9 *Surface Dressing*—The excess of the packing covers the wound with a thin layer of gauze. This, in turn, is covered with gauze dressings impregnated

This variation in technique we owe to a personal communication from Dr W V Cone,⁸ of the Montreal Neurological Institute, who developed it while serving in the No 1 Canadian Neurological Unit in Britain. The reader is also referred to a paper by Dr F W Shaver of the hospital, on The Primary Suture of Simple Mastoids.⁴⁷

†BIPP Bismuth subnitrate 1 part, powdered iodoform 2 parts, liquid paraffin about 1 part, or sufficient to make a thick paste

It is of the utmost importance that vaseline or *paraffinum molle* should not be used, as with such a vehicle an ointment results which will not adhere to the raw surface

with the emulsion. Finally, dry, fluffed gauze or preferably fluffed cotton waste is used as a reinforcement or padding for the whole wound area, and in sufficient quantity to make the largest feasible elastic compressible dressing, at least three inches in thickness (Figs 2 and 3). When plaster is to be used, the limb or part is now padded with sheet wadding (Fig 4).

10 *Occlusive Dressing*—Plaster of paris, the "pressure dressing,"* starch

FIG 5



FIG 6

FIG 5—Plaster encasement (circular bandage) completed except for foot in position on Hawley table

FIG 6—Completed plaster encasement elevated for drying

* The term "pressure dressing" has, we believe, achieved a special significance, especially in burn therapy and plastic surgery. First described in detail by Blair, Brown, *et al*,⁶ this dressing has been subsequently modified only in minor details to suit special purposes and techniques. Koch and Allen,³ Siler and Reid,⁴⁸ Neal Owens,⁴² and the authors,²⁴ in particular, have described the principles and use as applied to The Treatment of Burns and Skin Grafting.

bandages, elastoplast bandages or other alternative suited to the case are now used to encase the limb or part in such a way as to produce maximum fixation and optimum pressure. Not only the wound area but the joints proximal and distal to the wound must be encased. This reduces muscular action to an absolute minimum and consequently promotes lymph stasis. The plaster may be applied as snug moulds or slabs reinforced and fixed by circular plaster bandages, or the latter may be used throughout (Fig 5). In any event, the encasing plaster or alternative dressing must be applied with moderate pressure. The skill with which this is done allows for sufficient sustained pressure to prevent early loosening, although not sufficient to embarrass the vascular circulation. Such skill will only be acquired by personal experience. It should be pointed out here that when starch cinoline bandages are used, allowance is made for shrinkage and tightening as the bandage dries.

This may appear to vary widely from Trueta's⁵¹ unpadded plaster technique. Actually, however, the difference is more apparent than real, for the *large elastic* dressing under the plaster has essentially the same effect and is, we believe, a safer method for general use.

11 *Drying* of the plaster or starch bandages is accelerated by the use of a baker.

12 *Elevation*—It is well to allow elevation of the part at least until drying is complete and the circulation well established. During this period frequent inspection of the circulation of the protruding toes and fingers is necessary.

13 *Redressing* of these fresh trauma cases is discussed elsewhere, and details will be found in the Operational Chart. The week is the "time unit" but three to six weeks may be desirable especially when plaster is used. If fixation has been accomplished in the functional position, prolongation of the period between dressings is very unlikely to be followed by interference with joints or tendons.

PREEXISTING INFECTED WOUNDS AND SUPPURATING FOCI

B—The necessity for preliminary antishock and hemorrhage treatment rarely exists here, although frequently blood transfusions and/or infusions of 5% glucose solution are carried out before, during and shortly after operation. The necessity for the investigation of the state of the sugar metabolism in all cases of infection is emphasized as it is so frequently found to be disturbed at least temporarily. Determination of the sugar content of the blood during the fasting state may suffice. Often, however, a sugar tolerance test is required.

The usefulness of insulin in infections and wound healing has been stressed by one of the authors (Gurd)²⁰ and its adaptation to the individual case explained. Its usefulness in infections varies all the way from the necessary administration to protect the diabetic preliminary to operation to its rôle as an adjunct to wound healing and general debility treatment in chronic cases.

Sedation, anesthesia and local skin preparation are matters of hospital routine and individual choice.

Incisions must be so placed that maximum effect upon interstitial tension may be obtained with minimal damage to essential structures, and adequate in

size for good drainage purposes. As a general rule, multiple incisions should be avoided but rather one or few more extensive openings so fashioned that the effect indicated above may be obtained. Where necessary, Hilton's method of blunt dissection of deeper tissues is employed. All pocketing is broken down and in carbuncular types of inflammation the edges of the lesion are undercut to the limit of induration. In every case the guiding rule is to incise sufficiently not only on the surface for good drainage but, more importantly, to incise the fascial planes so as to both relieve all existing tension and anticipate its possible development or recurrence.

Cultures are taken at once. As much necrotic tissue and *débris* as can be judiciously excised is removed and the purulent contents of the abscess well evacuated. Allowance being made for good drainage, a gauze pack soaked in 5% sulfathiazole emulsion is now placed snugly in the cavity and the ends used to thinly cover the wound. The rest of the dressing procedure is carried out exactly as for fresh trauma.

TABLE I
LABORATORY REPORT
LABORATORY INVESTIGATIONS SHOWING THE CONCENTRATION OF SULFATHIAZOLE
IN LOCAL TISSUES TREATED WITH THE M G H EMULSION

Dressings Not Changed		
Elapsed Time After Treatment—Average of Estimations in Mg Per Cent (Total Sulfathiazole Only)		
Clinical Cases	M G H Laboratory	Independent Laboratory [*]
24 hours	120 mg per cent	124 mg per cent ¹
48 hours	78 mg per cent	76 mg per cent
72 hours	45 mg per cent	43 mg per cent
4 days	34 mg per cent	
5 days	30 mg per cent	
7 days	28 mg per cent	
Laboratory Animals	M G H Laboratory	Independent Laboratory [*]
24 hours	122 mg per cent	129 mg per cent
48 hours		65 mg per cent

Dressings are changed with about the same frequency in these cases as in fresh wounds. This may depend somewhat upon the amount of primary hemorrhage, necrosis or exudate, but the weekly timing has, for all practical purposes, proven satisfactory. This practice is carried out with both indoor and outdoor patients. It may be stated here that daily bacterial counts on the exudate, and chemical tissue analyses of biopsied material for sulfathiazole (see Table I) have served to confirm the safe period of bacteriostasis in these cases as averaging one week. In many cases, however, as in drained osteomyelitis or other cases where plaster is employed, it has been found advantageous to leave the encasement or dressing on much longer (up to four weeks). So far, we have not had cause to regret these longer intervals in a single instance though the odor may, at times, become objectionable. Finally, the possibility of delay or impairment of function must always be kept in mind after three or four weeks in a fixed position particularly if for any reason a physiologic position has not been possible.

^{*}These independent laboratory experiments were obtained through the courtesy cooperation and material assistance of Charles E. Frosst & Company, Montreal, Canada.

WOUND SUTURING

I PRIMARY 2 DELAYED PRIMARY 3 SECONDARY

1 *Primary suture* is only done on our early superficial wounds (within the first six hours), called "golden hours" by W W Keen,²⁹ when the risk of infection is minimal though contamination be always present (See the section on Bacteriology) This decision, also, will depend upon the anatomic site of the wound and, again, upon its nature Among the cases thus chosen for primary suture in the "golden hours" are minor lacerations in general, wounds of the hands and feet with tendon divulsions, chest wounds, wounds with vessel or nerve severance, wounds of the head, face and neck where the circulation is particularly good, and infection uncommon The last group must, also, be considered from the point of view of possible disfigurement which may occur if healing is inadequate The reader is referred to W H Ogilvie's³⁷ report on 5,000 cases of primary suture in which only 50 per cent showed good primary healing without infection Most of these cases it should, also, be noted were very carefully selected

2 *Delayed primary suture* is done in most other traumatic treatment cases, usually after the packing treatment has been employed for one or two weeks, that is at the time of first or less commonly the second dressing Up to this time, as a rule, wounds may be sutured without difficulty for the most part and, usually, without excision or freshening, as granulation is not excessive, and new epithelium is absent

3 *Secondary suture* implies a freshening or excision of the wound edges and is done for all cases in which delay is longer than two weeks, as when infection has been present This practice is followed even in carbuncles

In all deep wounds, especially of the extremities, buttocks, *etc*, and involving muscle, primary suture is not practiced regardless of the so-called "golden hours" and regardless of whether bacteriostatics have been used at the first dressing, or not It is not sufficient argument to state that "one can get away with it"

Skin Grafting—Just as suture has been carried out as primary, delayed primary, or secondary, in like manner we have employed skin grafting Quoting Dr John Gerrie, Plastic Surgeon at The Montreal General Hospital "Primary grafting may be done in many cases of sliced or avulsed wounds when dirt, infection and crushing are not present in undue amounts and the wound is not more than six hours old If these conditions prevail it is better to enclose the wound in an occlusive pressure sulfathiazole dressing and carry out a delayed primary graft at the end of a week or ten days If trauma and infection have been more extensive and at first dressing the wound is still not ready for grafting, one or two occlusive pressure dressings with sulfathiazole emulsion are carried out at seven- to ten-day intervals and a secondary graft done when a satisfactory bed is obtained, from three weeks onward (See Case B-4) It is emphasized here that the granulations are always scraped down to a firm bed Split skin grafts taken with the Padgett dermatome are

preferred and the thickness may be varied with the indications for weight bearing, texture, *etc*. The indications for 'pinch' and full-thickness grafts have become limited. This secondary grafting technique has been employed with success in open amputations when delayed or secondary suture cannot be done. The graft is applied as early as the third or fourth week to eliminate seepage from granulating areas at once and, thus, greatly shorten the convalescent period. By this method of handling early mobilization of the patient is achieved and the usual improvement in general condition results. Complete take of the graft is the rule. Following healing it is sometimes unnecessary to perform plastic reamputation to obtain a final result for prosthesis. Should this be necessary, however, much time, labor and, above all, morbidity will have been saved in any case." Case No. A-4, illustrates this adaptation of technique. This matter is referred to in greater detail in a recent article on "Burns" by Gerrie,²⁴ and further data is in preparation for publication.

SIX ESSENTIAL FEATURES FOR THE SUCCESS OF THIS TECHNIQUE

Experience by all those familiar with this method of surgical treatment has shown that the degree of success obtained depends upon certain essential factors, notably

1 *Timing of Each Step in Procedure*—All other factors are subordinate to this from the first to last. For example, the unwisdom of attempting surgical operation in fresh trauma before shock and hemorrhage is controlled is well known. On the other hand, if operation be delayed too long the risk of infection is enhanced. Hence the "golden hours" or 'safe period' are the essence of "timing." Again, to illustrate, is the success of relatively early skin grafting in burns, in the third and fourth week before granulation becomes excessive and the patient's general condition deteriorates.

2 *Efficient First-Aid in Emergency Cases*.—(a) *Control of Hemorrhage*. When a tourniquet is required it is imperative that the tourniquet be inspected by a doctor within half an hour. (See Blalock's¹² recent publication for elaboration.)

(b) *Prevention of contamination* by early application of a large, sterile gauze dry dressing. This dressing should rarely be interfered with until the case has reached the surgeon who is prepared to treat it. Application of a sulfonamide, preferably sulfathiazole, in powder or suspension form, may be carried out to advantage before the dressing is applied.

(c) *Minimization of shock* by alleviation of pain, protection from the elements and gentleness in handling the patient.

(d) *Splitting* of cases where necessary, with due regard to the nature of the injury, and due respect for the circulation of the part.

3 *Control of Shock and Hemorrhage*—Insofar as it is possible before definitive surgical treatment is begun. This rule does not preclude the necessity for minimal early procedures to save life, such as redressing for control of hemorrhage by means of ligation of large blood vessels and packing.

4 *Adequate Surgery Adapted to the Individual Case*—(a) In fresh

trauma this means enlargement, exploration and thorough wound excision. Evidence exists that when this is done within six hours of injury there is minimal risk of wound infection. Under special circumstances a period considerably longer than six hours may safely intervene between receipt of wound and operative care. Such conditions may include, among others, wounds received on a ship, on clean sandy beaches, and in manufacturing plants where infective material is absent. We believe that early adequate local application of sulfonamides prolongs the 'safe period' substantially.

(b) In all cases including infections this treatment implies provision for adequate wound drainage by the insertion of a snug pack of paraffin impregnated gauze. There is ample evidence to show that when the pack is impregnated with an oily material, such as liquid paraffin or vaseline, the drainage effect becomes more efficient. To meet this requirement for certain drainage and, at the same time, to give an effective degree of bacteriostasis, an oil-in-water emulsion of sulfathiazole was devised at the Montreal General Hospital. The formula for this is given elsewhere, while details of its preparation and clinical application have already been reported in the literature.

5 *Immobilization of the part* by plaster of paris, starch bandages, or 'pressure dressings'. In our experience it does not matter that "closed plaster" dressings be unpadded with this technique. On the contrary, we have found that a bulky dressing or padding under the plaster may be advantageous, providing the latter is applied with moderate pressure and, especially, if the bulky dressing is made semi-elastic, as by cotton waste. This dressing absorbs considerable exudate and continuous pressure is maintained throughout.

6 *Timing of Dressing*—The timing of change of dressing is most important. It will depend upon a number of things. Fundamentally, it is as infrequent as possible or necessary. In explanation of this statement one must consider all the reasons for the ordinary change of dressing. They may be listed as follows:

(a) Because of healing that has already taken place, as in superficial burns in six or seven days.²¹

(b) Because healing has taken place and prolongation of fixation may cause delay of functional recovery, as in tendon sutures, etc. (See Case No A-3.)

(c) Because prolonged fixation is conducive to healing, as in fractures (See Case No A-3.)

(d) Because exudate or hemorrhage is excessive and wound toilet is indicated, as in large trauma. (See Case No A-4.)

(e) Because bacteriostasis is exhausted by excessive slough, necrosis or exudate and renewal of the bacteriostatic agent is required, as in large infected areas or abscesses. The inhibitory effect of necrotic tissue and exudate on the bacteriostatic action of sulfonamides has been emphasized by such workers as Holder and MacKay,²⁸ and Strakosch and Clark.⁴⁹ These workers have demonstrated that when urea (carbamide) is added to the sulfonamides it effects some increase in the rate of necrosis of sloughing time. This, in turn,

prolongs the bacteriostatic effectiveness of the sulfonamide. Urea would thus appear to be a useful adjunct in extensive sloughing wounds. It must, however, be recalled that it does inhibit epithelization and, also, causes overgrowth of granulation tissue. Therefore, its use should be discontinued once the slough has separated. We have had no personal experience with the use of urea in our dressings.

REDRESSING—IN THE NORMAL COURSE OF EVENTS

When one surveys the reasons for ordinary redressing, it becomes apparent that the "timing" will vary somewhat with different types of cases and even with different cases of the same type. The experienced surgeon will, therefore, make his own decision in the individual case. The "end-point" of the individual dressing has been a consideration of prime importance in this work. In each case all of the above mentioned clinical factors are taken into consideration before reaching a decision. In addition, when splinting is not essential the authors have been influenced by the tissue concentrations of sulfathiazole and by the results of daily bacterial counts on the exudate, to change the bacteriostatic medium at approximately weekly intervals. It may be of interest to add that this same weekly procedure is regularly carried out on all surgical cases in the Out-Patient Department. The accompanying Operational Chart is offered as a guide to the procedure, to be interpreted by the reader as such, and not as a rigid standardized set of rules. It is hoped that it will be of use in this way, not only to the experienced surgeon but to the intern and nursing attendants less familiar with the technique of Closed or Occlusive Infrequent Dressings.

INDICATIONS FOR EMERGENT CHANGE OF DRESSING

Remarks on this subject may be prefaced by the comment that such indications are almost certain never to occur providing adequate surgery has been performed and when due regard has been given to all the other factors necessary for the success of the treatment.

The actual indications for changing the dressing and investigating the wound may be listed as follows: 1 Persistence of pain 2 Persistence of edema 3 Persistence or development of fever 4 Development of circulation difficulty

It is a fact that in all our cases during the past two years we have only encountered trouble in two cases, and in both instances it resulted from inadequate surgery following an error in diagnosis. These failures were therefore, due to the human factor, and not the technique. In both instances proper surgical measures, promptly taken, gave relief and permitted continuation of the original treatment with no untoward final result. One of the cases is given in some detail. (See Case No. B-3.)

THE VALUE OF CHEMOTHERAPY

THE RÔLE OF SULFONAMIDES AND OTHER BACTERIOSTATIC AGENTS

Chemotherapy in wound treatment is not new. Rather it is very ancient. Without historic reference in detail, one has only to recall Lister's¹ antiseptic

technique to appreciate the importance attached, throughout medical history, to some local method of destroying bacteria and controlling infection B I P P and its progeny, Z I P P and Z I S P, and certain analines, are the more important contributions in this field. The local use of sulfonamides has more recently opened a new avenue of thought along this line and has probably done more to stimulate general interest in the subject than any preceding agent. In 1941, as previously stated, an oil-in-water emulsion of sulfathiazole was developed at The Montreal General Hospital (see formula) and first applied clinically to the closed plaster technique by one of the authors, Ackman^{1, 2}. The wide subsequent use of this vehicle for sulfonamide therapy at the hospital, and elsewhere, since that date, has proven its value. Not only is it an excellent medium for local sulfonamide administration but it, also, has the additional advantage of providing a reservoir of the sulfonamide in the pack in contact with the wound surface. This results in a more prolonged delivery for the bacteriostatic agent than when used in powder or crystalline form or in aqueous suspension. At the same time, the oily medium provides the type of "curtain drainage" which is required for the open treatment of wounds under closed plaster or other occlusive dressing. It is not intended to give all the details of our experience with the emulsion at this time. The reader is referred to the original papers on the subject in the current literature. It is considered advisable, however, to restate certain facts regarding the emulsion.

1. An oil-in-water emulsion was chosen as vehicle for the reasons above stated and because, since the sulfathiazole is known to be in the water phase, it is readily deliverable to the local tissues.

2. Sulfathiazole was chosen because of all the sulfonamides used, it has the greatest bacteriostatic effect, and is the most efficient against 'the *Staphylococcus pyogenes*'⁹. Compared with sulfadiazene it is much more soluble in serum and, therefore, more readily absorbed. It is, also, much more readily excreted. Again, by comparison, sulfanilamide, being much more soluble, is too rapidly absorbed to allow for the prolonged and relatively high local tissue concentrations from sulfathiazole. For the same reason, there will be risk of too high blood concentrations with sulfanilamide.

3. Because of the presence of triethanolamine in the emulsion, a very much higher percentage of sulfathiazole is in true molecular solution than when the crystals are merely suspended in water or serum. To be explicit, about 26 per cent of the sulfathiazole is in molecular solution which is about 800 times the solubility of this material in water at the same temperature.

4. The pH of the emulsion in the pack ranges from 7.6-8.6, which is satisfactory from a wound-healing and bacteriostatic viewpoint.

5. The local tissue concentrations have been estimated from excised tissue and found to be sufficiently high to maintain efficient bacteriostasis. The technique used is essentially that described by Reed and Orr⁴⁰. These concentrations (Table I) afford an efficient degree of local bacteriostasis for at least a week and probably for a slightly longer period. The period during which

the tissues of the wound are most vulnerable to pyogenic invasion is thus well covered. Moreover, renewal of the emulsion pack and dressing reestablishes the protection.

6 This bacteriostatic effect has been confirmed by daily bacterial counts from the wound-pack and serum, as well as by critical clinical observation.

7 In spite of the high local tissue concentrations of sulfathiazole, the level of this chemical in the blood has never in a single case been found to be higher than 3.5 mg %—even when as much as 15 ounces of the emulsion has been used in packing a large wound, such as open amputation of the thigh or in the dressing of a 50 per cent burn. The usual or average blood level is much lower than 3.5, and the reports regularly show only a trace in the blood when large amounts of the emulsion are used (Table II).

TABLE II
BLOOD LEVELS OF SULFATHIAZOLE IN LOCAL TISSUES TREATED WITH THE M G H EMULSION

Clinical Cases	Dressings Not Changed	
	M G H Laboratory	Independent Laboratory*
1 hour	Total 3.5 mg per cent	
2 hours	3.1 mg per cent	
3 hours	3.0 mg per cent	
12 hours	1.3 mg per cent	
24 hours	None to trace only	
Laboratory Animals	M G H Laboratory	
		Independent Laboratory*
1 hour		12.1 mg per cent
2 hours		7.6 mg per cent
3 hours		3.5 mg per cent
4 hours		1.5 mg per cent
5 hours		Trace only
6 hours		None

8 No single instance of either toxic blood, hepatic or other serious reaction has occurred in several hundred cases.

9 No single instance of renal complication has occurred from this local therapy.

10 With regard to hypersensitivity skin rashes, we have this to say. The total number of cases with a general rash is twelve in several hundred, and the local rashes have been about the same in number. It should be noted that in over 150 burns so treated, this local reaction has only occurred once. In this instance it can be emphasized that the case was not treated by the "pressure dressing" technique we have advocated but received rather casual treatment with change of dressing every day or two for five weeks in the Out-Patient Department. This hypersensitivity may be preexistent (three cases) without previously known sulfonamide treatment or it may be acquired after periods of treatment varying from 1-12 weeks. The hypersensitivity is now known to persist for months at least but, in at least two cases, has disappeared after a year. When it does occur, it is specific for the sulfathiazole, and any other sulfonamide may be satisfactorily substituted in the emulsion. These rashes may be uncomfortable at times and even occasionally annoying to the patient.

*These independent laboratory experiments were obtained through the courtesy cooperation and material assistance of Charles E. Frosst & Company, Montreal, Canada.

and surgeon but they have never been accompanied by any serious toxic effect and only occasionally by febrile reaction

11 Clinically, we are satisfied that no safe oral administration of the drug can produce as good local bacteriostasis.⁹ When used orally the amount given the patient is limited by the safe blood level. The resulting local tissue or burn level cannot become higher than the blood level. The level thus obtained from oral administration can never compete locally with the levels obtained from direct topical application.

12 The stability of the emulsion in containers has been tested at temperatures ranging from plus 120° F down to minus 97° F and has been found to be satisfactorily maintained.

SCOPE OF TREATMENT

TYPE OF CASE, WITH ILLUSTRATIVE CASE REPORTS

A Fresh Trauma—Contaminated, or Potentially Contaminated

- (1) Extensive lacerations or avulsion injuries
- (2) Tendon or nerve divulsions
- (3) Compound fractures and fracture-dislocations
- (4) Open amputations or reamputations
- (5) Burns and donor areas
- (6) Crushed hand or foot

B Preexisting Infections

- (1) Osteomyelitis
- (2) Large soft tissue abscesses
- (3) Infections of the extremities (palmar abscesses)
- (4) Acute or chronic surface ulcers, such as ulcer cruris and ulcer decubitus
- (5) Carbuncles
- (6) Abdominal and thoracic abscesses

ILLUSTRATIVE CASE REPORTS

Case A-3—A—Severe compound fractures—both bones of the left forearm. Service of Dr. George D. Little, A.D., suffered a severe compound fracture of the left forearm from a machine accident, and was admitted within one hour of the accident (Fig. 1). Circulation and nerve function were intact. Shock and hemorrhage were shortly controlled, allowing operation to be carried out within two hours of admission. The wound

PLATE I

Case A-3 Compound Fracture of Both Bones of Forearm

A Preoperative state

B Three months after accident. Encasement discarded and function commenced

Case B-4 Chronic Leg Ulcer (Micro-aerophilic Streptococcus)

C Condition on admission to hospital

D Eight days after admission with pressure dressing. At this point redressed with elastoplast compression dressing and mobilized

E Twenty days later dressing changed

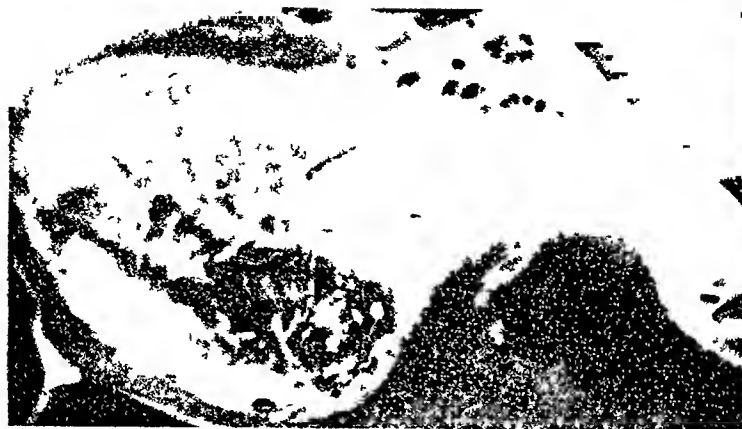
F Dressing removed at 48 days from the time of admission to hospital. Advised to wear elastic stockings

A

C



PLATE II



E

F

required considerable muscle debridement. Reduction of the fractures was retained without mechanical fixation because the sharp ends of the bones caught. After packing gauze impregnated with sulfathiazole emulsion, a padded plaster of paris encasement was applied, including arm, forearm and hand. Postoperative course was uneventful. The first change of dressing was done at six weeks (Fig 2), when a secondary suture was carried out. Roentgenograms showed no evident bone disease.

At two months, the wound was healed but continued arm fixation in plaster was necessary as bony union was incomplete. At three months, function has been commenced without occlusive dressing. This is the condition at the present time. There is no nerve partial paralysis but muscular weakness is still marked and requires physiotherapy.

Case A-3—B—Compound dislocation of elbow—M G H No 2829-42 J O, female, aged 46, suffered a severe compound dislocation of the left elbow, without fracture. The patient was admitted by ambulance, the arm having been wrapped in a clean towel and bandaged. The circulation and sensation of the hand and forearm were intact. Shock was moderate and quickly controlled by plasma, as bleeding had been minimal. The dressing was not disturbed until the patient reached the operating room, less than three hours after the accident. Under anesthesia, examination showed that the joint had been completely distracted. The lower end of the humerus protruded from a large wound on the external surface of the arm. The wound was treated by the technique described herein, considerable excision being necessary as much muscle had been destroyed. When the dislocation was reduced, the capsule of the joint was approximated with a few interrupted catgut sutures which did not completely close it. The wound was packed and the skin edges approximated. Over the packing a large dressing and cotton waste padding was placed. A plaster shoulder cap was applied, including forearm and hand. The patient left the hospital five days later.

The first change of dressing was done three weeks after operation, when repacking was carried out. Six weeks after the injury the second dressing was done, all packing removed and a secondary suture carried out. Again, plaster was applied, this time, also, for three weeks. On its removal, two months after injury, joint movement was commenced. At three months, the wound was completely healed and movement of the elbow was as follows: Flexion 75% restored, extension 90% restored, pronation and supination almost normal. At four months, 90% function was present in a painless non-edematous arm.

Case A-4—Severe crush injury of whole thigh and leg requiring amputation. J I, age 50, suffered a machine injury which laid open the inner side of his left thigh and leg from the femoral triangle down to the calf. The adductor and other muscles, as well as the femoral vessels and nerve, were severed and crushed in the lower third of thigh. On admission, a very efficient large first-aid dressing covered the leg, thigh and hip. A tourniquet had not been necessary as the crushed vessels thrombosed at once. Oozing, however, had been considerable. To combat shock-hemorrhage continuous transfusions of fresh blood were required, 5,000 cc being given in the first 48 hours.

PLATE II

Case A-4—Severe Avulsion Injury of Thigh and Leg

- A Preoperative state
- B Amputation stump after nine days. Encasement off and packing removed
- C Stump granulations on 25th day after amputation. Ready for grafting
- D First dressing of graft after 14 days, showing almost complete take

Case B-4—Chronic Leg Ulcer

- E Preoperative state
- F Completed graft after 14 days, and 35 days after first operation

Oxygen and other emergency measures, as on the chart, were carried out Six hours after the accident it was considered necessary to inspect the wound in view of the absence of leg circulation Cyclopropane permitted only a momentary inspection and ligation of the large vessels (On ligation, venous bleeding occurred at the knee *via profunda femoris*) No other surgery was possible as the patient's condition became very grave A large sulfathiazole emulsion pack was quickly sutured in place and a padded plaster applied On recovery, 1500 units of A T S and 40,000 of antigas serum were given After 48 hours of further successful antishock hemorrhage treatment it was apparent that leg circulation below the knee had ceased and that amputation was necessary His general condition was excellent by now Open amputation was carried out through the lower third of the femur, leaving such flaps as were possible, long on the lateral side and very short on the medial surface of the thigh A considerable portion of the adductor muscle group was excised The very large open stump was first flushed with a 5% suspension of sulfathiazole microcrystals, then packed with sulfathiazole emulsion gauze, and a pressure dressing with plaster applied to the hip only Postoperative recovery was entirely uneventful only occasional transfusion being given during the next few days No evidence of general sepsis occurred and on the ninth day the dressing was changed, under anesthesia Some further slough was removed and the same plaster dressing was reapplied Further dressings were done on the nineteenth and twenty-eighth days with plaster On the thirty-sixth day, the open wound granulations were removed and split-skin dermatome grafts applied by Dr J W Gerrie, and the stump enclosed in a "pressure dressing" On the fiftieth day, this was removed and a 99% "take" found, the wound being practically healed A small skin graft was used to cover the remaining bare area The whole wound was healed on the seventieth day, when an elastocrepe bandage was first used in preparation for an artificial limb

Case No B-1—Acute osteomyelitis—M G H No 4618-42 A S, female, aged 13, was admitted in *extremis*, three weeks after a minor superficial infection in the right leg, with all evidence of acute osteomyelitis in the proximal end of the left humerus and with staphylococcal septicemia She was comatose and her condition was considered very grave Operation was delayed until 24 hours after admission, during which time staphylococcus antitoxin and sulfathiazole were given intravenously with excellent effect The periosteum over the upper end of the humerus was found to be elevated by pus The shaft was drilled and similar pus obtained The wound was treated by the technique described herein and a plaster shoulder cap applied including the forearm but not the hand Postoperatively, the patient's general condition promptly and decidedly improved and blood cultures became completely negative on the day after operation The first redressing was done at three weeks, and roentgenograms showed extensive involvement of the humeral shaft but a normal shoulder joint Subsequent redressings were carried out at monthly intervals for four months when, on roentgenologic examination, two sequestra were found and removed Local occlusive dressings fortnightly with elastoplast have since been entirely satisfactory Six months after the original admission there is only a small draining sinus at the site of the original incision and function of the arm is being restored Roentgenologic examination is satisfactory and the shoulder joint has never been involved

Case B-3—Infections of extremities (thenar and web space infection)—M G H No 6465-42 A K, male, age 15, was admitted with a swollen hand resulting from an infection of the web space between forefinger and midfinger in consequence of an infected blister There were no definite signs of infection of the palmar or thenar space The web space was incised and considerable pus evacuated It was packed open and the whole hand immobilized in padded plaster The case presents the following point of special interest Contrary to the rule, the fever did not subside and the patient complained of increasing pain in the hand Following the rules, the encasement was then removed

after 48 hours, when a well-developed thenar space abscess was found. It was incised and packed. The padded encasement was reapplied. The patient's temperature promptly dropped to normal overnight and the further progress was uneventful. As is customary in this type of case, he was allowed up at once and left the hospital on the third post-operative day. The dressing was changed and the pack removed on the tenth post-operative day. Only one redressing with plaster, for a further period of two weeks, was necessary to complete healing. Functional recovery ensued.

Cases B-4—Chronic leg ulcer (vascular) B G, male, age 72, was admitted with a chronic leg ulcer of five years' duration which had received little or no treatment. During the last six months, it had extended considerably and when seen the whole lower third of the leg on its anterior half was deeply ulcerated with necrosis of the exposed tibialis anticus tendon and muscle belly. At operation, all slough was excised and the wound treated as described herein. A padded plaster was applied from toes to mid thigh.

At three weeks, the dressing was changed and granulations found to be healthy. The granulations were scraped off and a split-skin dermatome graft applied by Dr. John Gerrie. A large "pressure dressing" was applied. This was removed at ten days, revealing a 100% take. Subsequently no dressings were applied but elastoplast used to control some persistent leg and foot edema, on walking. Four weeks later this was discontinued. Check-up, after six months, shows a good result.

A second chronic leg ulcer in V C, a female age 52, had no vascular pathology but revealed a microaerophilic streptococcus (Meleney) on culture. This had recurred intermittently for fifteen years and had been currently chronic for two years. She had a compression dressing with sulfathiazole emulsion applied for nine days in bed. She was then mobilized with a somewhat thinner pressure dressing covered with an elastoplast bandage. These dressings were renewed at appropriate intervals until healed on the 48th day. At one year later there has been no recurrence.

Case B-5—Carbuncle on back J P. A large carbuncle situated in the interscapular region of the back, in a nondiabetic, was treated by crucial incision and excision. The wound was packed and an occlusive elastoplast adhesive dressing applied. It was redressed on the sixth and twelfth days. On the eighteenth day all packing was removed and, on the twenty-first day, excision and secondary suture were carried out. All dressings were removed on the thirtieth day, the wound being healed. Identical results have been obtained in diabetic patients using insulin to obtain and maintain control from the outset.

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CONTINUOUS CAUDAL ANALGESIA IN SURGERY*

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ON OCTOBER 10, 1941, continuous caudal analgesia was first applied clinically, being used to relieve pain for an operation upon the lower extremity. During the next two months it was used for ten other patients and the lessons learned were applied to obstetrics^{1, 2}. Since then numerous patients have been given this form of analgesia for all types of operations upon the trunk and lower extremities and for the relief of pain in labor and delivery^{3, 4, 5, 6}. It is the purpose of this paper to describe in detail the fundamental aspects of the method as applied to surgery, to outline improved technics of administration, to cite certain therapeutic applications, and to bring up to date the results of our experience with the method.

Because continuous caudal analgesia is safe and controllable in both extent and duration of effect, we believe that it has extended the field of regional anesthesia and, thus, indirectly extended the field of surgery. To understand the application of this new principle, it is necessary to review the anatomy involved, and since caudal analgesia is a form of epidural anesthesia, a consideration of the epidural space is in order.

The *epidural space* is that portion of the vertebral canal not occupied by the dura and its contents. Superiorly it ends at the foramen magnum where the dura mater divides into two layers, one becoming the endosteum of the skull and the other the pachymeninx over the brain. Within the canal the dura lies in close apposition to the periosteum of the posterior aspects of the bodies of the vertebrae, and laterally it extends with each nerve root. Posteriorly it has no connections. As the nerve trunks emerge from the intervertebral foramina, a curtain is formed over the opening by connective tissue fibers arising from the intervertebral ligaments and fusing with the epineurium. Occasionally we have noted, in dissecting these epidural spaces, that a median fenestrated fibrous raphe is produced by prolongation of the dura along the minute nerve fibers extending upward between the spines and to the periosteum of the vertebral arches. In one instance we found clinical evidence of adherence of the dura to the promontory of the sacrum.

Thus, the dural sac with its contents of spinal cord and cerebrospinal fluid almost completely fills the vertebral canal, allowing only three to six millimeters between the ligaments and the sac itself. Approximately nine-tenths of the space lies lateral and posterior to the dura and is filled with adipose tissue in a solid and semisolid state and with a rich plexus of blood vessels consisting of the veins of the internal vertebral plexus¹.

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shape of this opening is triangular, the apex of the triangle being superior. The apical angle varies from 20 to 60 degrees and its extent is determined by the width of the hiatus. Due to failure of fusion of the 3d, and perhaps higher, sacral laminae, in addition to the 4th or 5th, the hiatus may extend a greater distance upward. In some instances it may be placed entirely at a high level, so that the floor is formed by the body of the 2d or 3d sacral vertebra rather than the 4th or 5th. Due to intermittent failure of fusion, additional openings

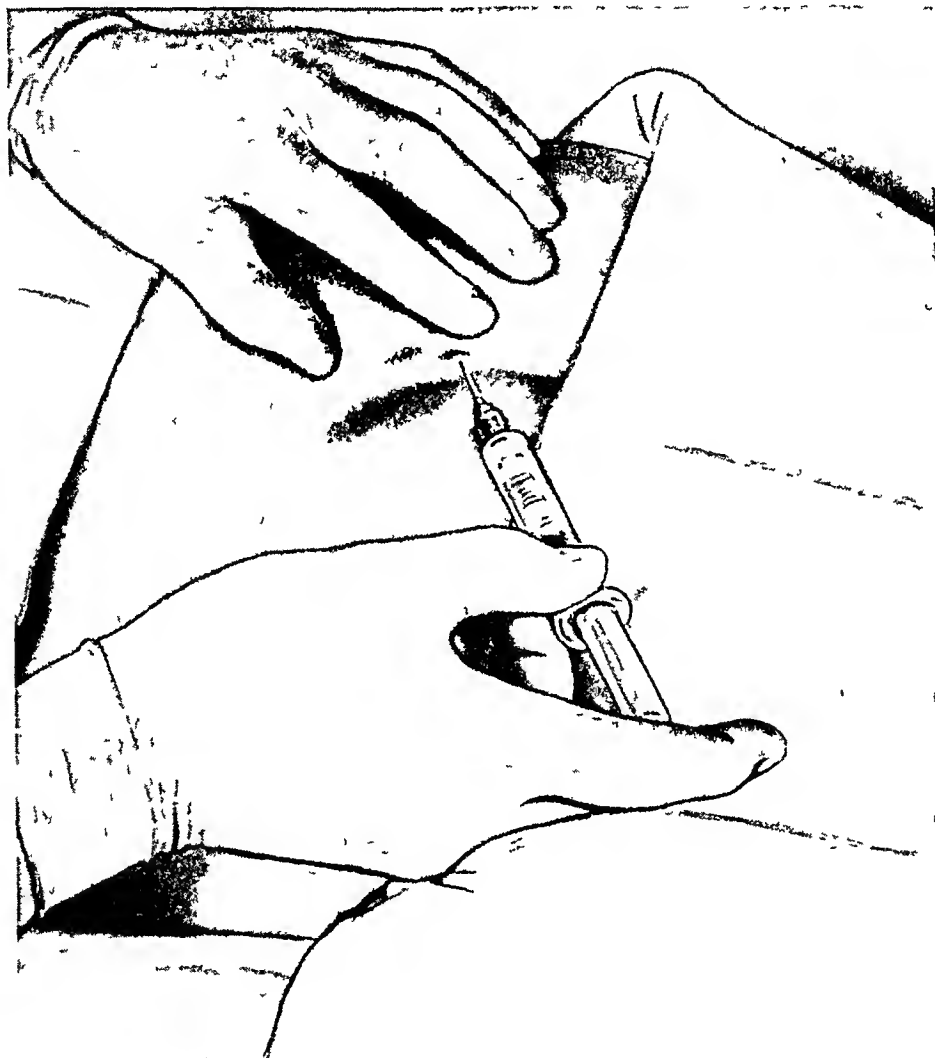
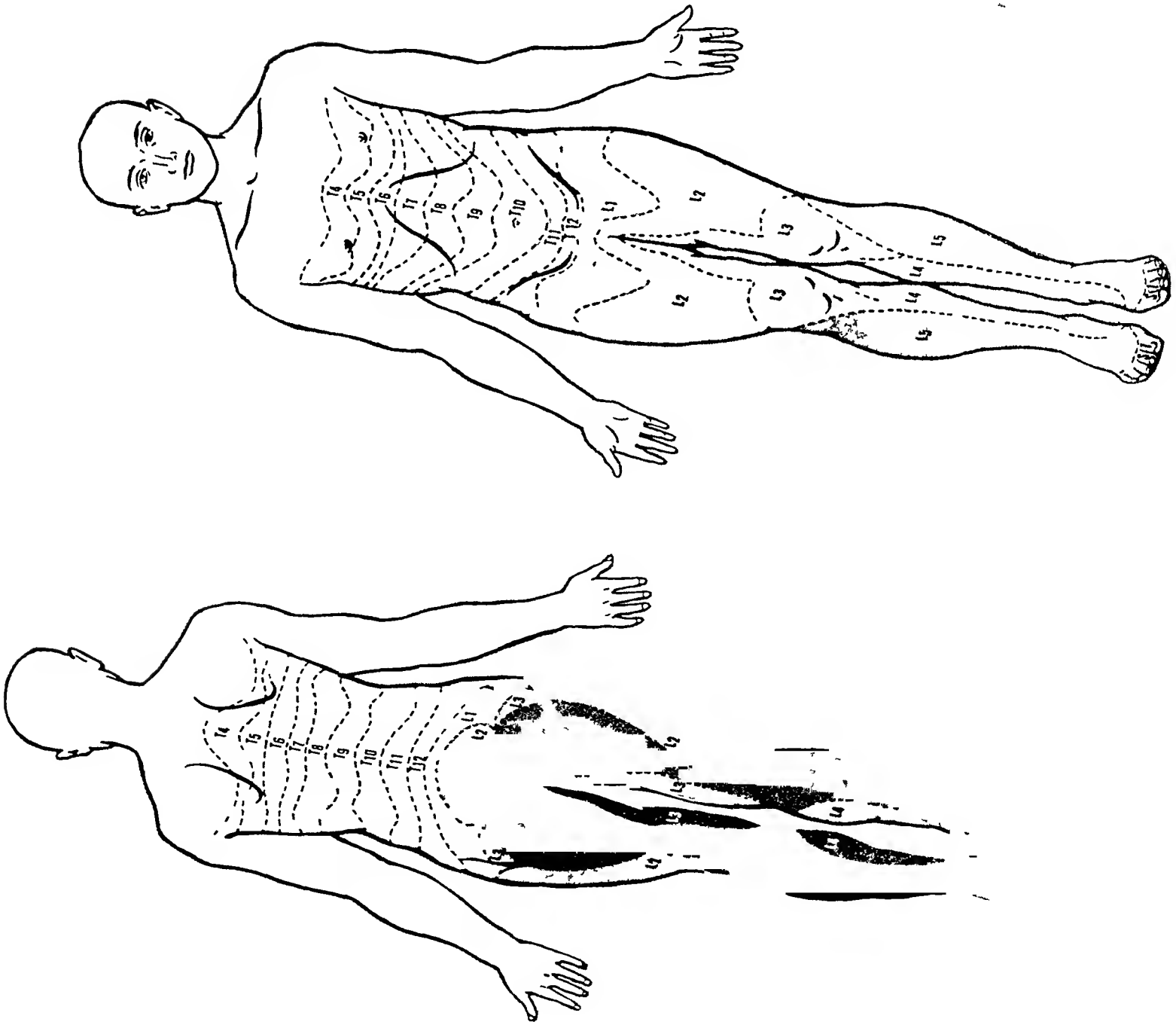


FIG 2—Raising skin wheal immediately below sacral hiatus

into the sacral canal may exist together with a more or less normally placed hiatus. In some sacra no roof is present over the canal, in which case the hiatus may be said to extend from the usual location to the beginning of the lumbar epidural space. Bony overgrowths of adjacent structures may entirely obscure the hiatus, a flattened 4th sacral spinous process being the common offender.

The practical importance of these facts is evident. A knowledge of the variations of the sacral hiatus is necessary in order to introduce a needle into



- 10 cc. includes S3 and Below
- 20 cc. includes L5 and Below
- 25 cc. includes L2 and Below
- 30 cc. includes T11 and Below
- 40 cc. includes T8 and Below
- 50 cc. includes T6 and Below
- 60 cc. includes T4 and Below

the sacral canal of all subjects. Lack of this knowledge is an obstacle to the beginner and is the cause of early failures.

From a consideration of the structure of the epidural space as described, it can be visualized that an anesthetic solution spreads posteriorly up into the space and at the same time extends laterally through the sacral and intervertebral foramina. It first affects the posterior roots by reason of their proximity but soon spreads to the united roots to produce motor effects. The autonomic is readily anesthetized because of the small caliber of its fibers and the absence of a myelin sheath. Because of the fibrous curtain over the intervertebral foramina, fluid injected into the epidural space must infiltrate into the nerve roots or pass through the connective tissue network into the paravertebral spaces in order to produce effects.

With continuous caudal analgesia, as with other forms of regional anesthesia, minimal changes in vital functions occur. However, certain physiologic aspects require mention.

Loss of sensation under the influence of caudal analgesia occurs much slower than under spinal anesthesia. Shortly after administration of the initial dose of anesthetic solution by the caudal route, loss of sensation can be noted on the buttocks about the sacral hiatus. As the sacral and lumbar nerves are successively affected, loss of sensation proceeds over the buttocks, up over the sacrum, and anteriorly over the perineum to the abdominal wall. At the end of five minutes it is possible to demonstrate saddle analgesia from an initial dose of 30 cc. of 1.5 per cent metycaine solution. The appearance of saddle analgesia, or bilateral sensation loss, inferior to the hub of the caudal needle is a valid indication that the needle is situated within the sacral canal. If such sensation loss is present after five minutes with the dose described, the needle is within the sacral canal; if such loss is absent, the needle is not within the canal. The extent of saddle analgesia that follows an initial dose of 30 cc. of 1.5 per cent metycaine is a valuable guide to individual response to caudal analgesia.

Within ten minutes after administration of a dose of metycaine as described, there is usually analgesia of the scrotal or vulval area, and at the end of thirty minutes the level of effect has reached its maximum height which is to the umbilicus (10th thoracic segment) in the average subject. The height to which such a dose may rise is subject to individual variation. The maximum is to the xiphoid and the minimum to the symphysis pubis.

Dissociation of loss of sensation occurs with this form of analgesia. The sensation of intrinsic pain is first to be obliterated, and this is followed shortly by loss of appreciation of extrinsic pain. As the effect of the drug proceeds, there is loss of sensation of touch and loss of appreciation of temperature. One can map out areas in which loss of sensation to extrinsic pain is obtained but in which touch can still be appreciated as analgesia progresses. This touch perception is graded from grosser to finer forms. Loss of pain sensation is present to three segments higher than loss of touch when the maximum level for a given dose has been reached. For surgical procedures it is necessary to

make sure that the field is anesthetized to the extent that touch can no longer be appreciated. While some patients will permit operation in a field in which touch can be felt, most prefer to feel nothing.

Motor roots are affected shortly after sensory roots by anesthetic solutions in the epidural space. With large doses of solution, motor effects are produced more rapidly and are more profound than with small doses. It is believed that the solution diffuses through the intervertebral foramina, affecting the sensory roots first but soon producing motor effects by penetration of the motor root or formed nerve.



FIG 3—Infiltration with fascia needle down to ligament with anesthetic solution

It is quite possible to produce satisfactory surgical analgesia and, at the same time, retain a certain amount of motor control. The use of continuous caudal block in surgery has demonstrated that motor nerve paralysis is unnecessary for production of *muscular relaxation*. If sensation, indeed, if pain perception alone, is interrupted to the muscles of the abdominal wall, for example, adequate relaxation follows. Therefore, relaxation obtained from caudal block is always excellent when adequate levels of sensation loss are produced. Relaxation so produced constitutes one of the principal advantages of caudal block as a surgical anesthetic. Thus, continuous caudal analgesia is

especially valuable for the seriously ill patient, providing widespread muscular relaxation yet maintaining the inherent safety of a nerve block procedure

The question of *intestinal tonus* is of interest to surgeons when considering an anesthetic method. Because it reaches only the sympathetic supply to the gastro-intestinal tract, caudal block produces increased intestinal tonus in the absence of irritative or obstructive lesions of the bowel. In the presence of irritation or obstruction, intestinal activity and tone is similar to that noted with spinal anesthesia. In elective or interval operations, the intestines lie quietly in the abdominal cavity so that operative procedures are facilitated.

Respiration is not affected by high caudal block. With solutions of customary strength, such as 1.5 per cent metycaine, one obtains surgical analgesia in the upper thoracic segments without evidence of intercostal paralysis. It seems that as anesthetic solutions are forced higher into the epidural space they tend to produce sensory effects without motor paralysis, due perhaps to dilution of the anesthetic solution. Patients have been observed with anesthesia of the entire distribution of the ulnar nerve from high caudal block with no effect on the diaphragm.

The effect of caudal block on *blood pressure* depends on three factors, namely, rate of absorption of the drug, rapidity of extension of sympathetic nerve paralysis, and final height of effect.

In the average subject in whom low caudal block is employed, as in obstetrics, blood pressure effects are minimal. The rate of absorption is low, and high levels with extensive sympathetic paralysis are not produced. If a vein is pierced at the beginning of the procedure, some of the solution may be forced into the general circulation so that blood pressure falls. If large doses are employed after a bloody tap, increased amounts of solution may be absorbed, with marked fall in blood pressure and other toxic phenomena. Thus, it is important in poor risk patients and in cesarean section to avoid a bloody tap when administering caudal block.

Fall in blood pressure may also be produced by sympathetic nerve paralysis alone. In low caudal block the extent of sympathetic effect is insufficient to produce marked change. If a high level of analgesia is produced rapidly, compensating factors which help regulate arterial tension may be overcome so that a marked and precipitous fall occurs. With careful technic and with regulation of rapidity of rise of analgesic level, it is possible to produce analgesia in the 1st thoracic segment without change in blood pressure.

Fall in blood pressure as produced by caudal block, when absorption of drug is not a factor, does not represent the same physiologic change as a similar fall produced by spinal anesthesia. Marked lowering of arterial tension from spinal anesthesia is usually accompanied by evidence of shock and anoxia. Such is not the case with caudal block. We have observed that blood pressure may fall so low as to be unobtainable with a sphygmomanometer without signs of cardiac embarrassment, changes in skin humidity or changes in the color of the blood. In this circumstance the patient falls asleep but suffers no ill effects. The pressure responds readily to the common vasoconstrictive

finely divided state. This is diluted just before use with physiologic saline solution. Epinephrine must be added when this drug is used for regional anesthesia, a concentration of about 1/200,000 being satisfactory. We have employed pontocaine for epidural analgesia by the caudal route in strengths of 0.2 to 0.25 per cent, with epinephrine. More than 150 mg but probably less than 250 mg may be given at a single dose. In our experience the action of pontocaine has been somewhat erratic. A dose of 30 cc of 0.2 per cent solution, with addition of epinephrine, will usually produce a low caudal block of surgical intensity after forty minutes. This effect will persist from

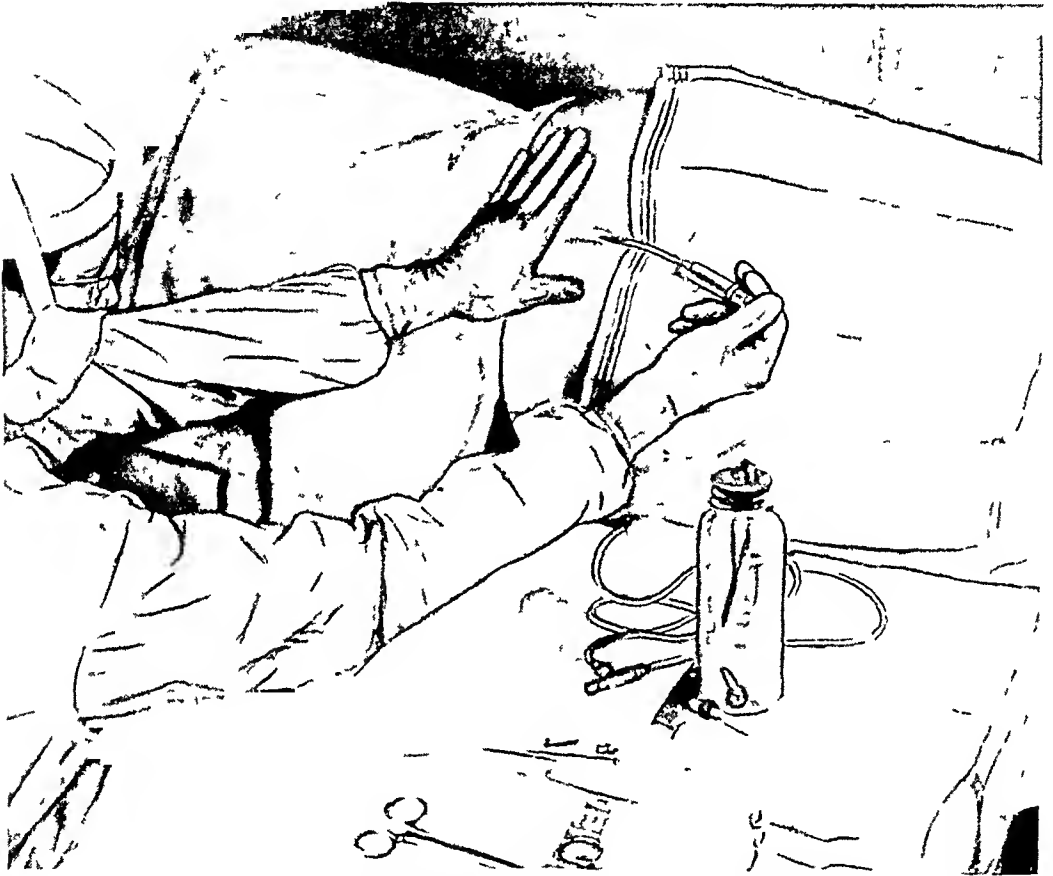


FIG 5—Injection of test dose of 8 cc of solution into sacral canal with the palm of the left hand firmly pressed over sacrum in an attempt to identify extrasacral injection.

fifty minutes to six hours. It seems that pontocaine sometimes only partially blocks nerve conduction. Further work with pontocaine may prove it useful as an epidural anesthetic for relief of postoperative pain. An optimum concentration, as yet not found by us, may be necessary for best results.

Metycaine was synthesized in 1926. It is a fine white powder, soluble in water one to one, and freely soluble in alcohol and chloroform. In aqueous solution it is faintly acid. In the strength of 1.5 per cent in physiologic salt solution it does not lysis red blood cells and appears to be nonirritating to the tissues locally. It is employed for local, regional, and spinal anesthesia. Eli Lilly and Company manufactures it and furnishes it in bulk powder, in solu-

tion, in ampules, and in other forms. The most convenient package for use in caudal analgesia is an ampule containing 5 cc. of 20 per cent solution (1 gram of drug). Solutions may be prepared from this ampule by dilution with sterile physiologic saline. Solutions prepared from the powdered drug may be autoclaved or boiled, and stored without deterioration. Epinephrine may be added to solutions prior to use. A concentration of approximately 1/300,000 is adequate. The total amount of metycaine tolerated at a single injection epidurally is in excess of one gram but is less than three grams. This drug seems to be rapidly absorbed and eliminated. Considerably greater amounts may be administered by serial injection. We have used doses of five grams, or over, during six-hour periods without immediate or delayed toxic effect. One and one-half per cent metycaine solution, with addition of epinephrine in the strength of 1/300,000, produces prompt, complete, nerve conduction block. Thirty cubic centimeters of this solution administered into the epidural space through the sacral canal produces a low caudal block of surgical intensity after ten to fifteen minutes. This effect may be depended upon to persist for a minimum of one hour and may last for two hours.

The local anesthetic drugs are apparently metabolized in the liver. They are broken down or conjugated or otherwise "detoxified" there, and the metabolites are rather promptly excreted in the urine. Even after very large doses, almost all excretion has taken place within twenty-four hours, most of it within the first eight hours. Little or no unchanged drug is to be found in the urine.

As a group, the local anesthetic drugs are central stimulants of the convulsive type. Toxic symptoms may follow intravenous injection or overly rapid vascular absorption. Systemic reactions fall into three general types, characterized respectively by (a) Signs of central nervous irritation, such as restlessness, apprehension, loquacity, sweating, pallor, palpitation, nausea, tremors, and in the more severe cases unconsciousness and convulsions, (b) circulatory collapse or shock manifested by sudden fall in blood pressure, bradycardia, and in severe cases stoppage of the heart, and (c) true allergic symptoms such as bronchospasm, urticaria, or angioneurotic edema. Parts of the first two types may occur together. There is some evidence that a rapid rise in blood level, as with inadvertent intravenous injection, is more likely to produce the second type of reaction, and that the slower attainment of a high level, such as after infiltration of overly large doses, tends to produce the first type. The rule is by no means universal, however, and different individuals appear to vary greatly in their susceptibility. The true allergic type of reaction is rare.

The convulsive type of reaction can be prevented by the previous administration of sedative doses of the barbiturates. These drugs, given intravenously, are of some value in treatment of convulsions, but treatment is less satisfactory than prevention. For the collapse type of reaction the barbiturates have little value, and pressor drugs, cardiac and circulatory stimulants, plasma, and measures used to treat other types of shock should be employed.

Table I summarizes pharmacologic effects of interest. Procaine in 1.5 per cent concentration, with addition of epinephrine, is a satisfactory solution, but increased incidence of mild toxic effects from its use in our hands led us to seek another drug. We do not prefer pontocaine because of apparent lack of prompt, uniform, complete sensory block. For the present we continue to recommend metycaine 1.5 per cent in physiologic saline, with epinephrine 1/300,000, as the drug solution of choice for continuous caudal analgesia in surgery. For therapeutic caudal block epinephrine is omitted.

Certain principles concerning control of level of analgesia and methods of determining dosage for a given patient have become apparent as more experience has been gained with the use of continuous caudal analgesia in surgery.

One advantage of this method is that it is controllable in level, depth, and duration of effect; this feature is unique in the field of regional analgesia, but stems from the continuous feature of spinal anesthesia devised by Lemmon.⁷ Control of level of analgesia in caudal block is exercised by regulation of the quantity of solution given at any one time, by the speed with which the injection is given, and by taking advantage of the effect of gravity. The height to which effect is produced is proportional to the amount of solution administered.

TABLE I
PHARMACOLOGIC EFFECTS OF LOCAL ANESTHETIC AGENTS

	Procaine*	Pontocaine*	Metycaine*
State of sensory block	Prompt and complete	Slow in onset Sometimes incomplete	Prompt and complete
Period of effect	20 min. to 1½ hours	50 min. to 6 hours	1 to 2 hours
Unpleasant sensations†	None	None	None
Elimination of drug	Rapid	Rapid	Rapid
Toxicity from routine use	Increased mild reactions	Few mild reactions	Few mild reactions
Resumption of nerve function	Complete	Complete	Complete

as a continuous injection. Small amounts given as single doses serve only to reinforce analgesia at low levels. Larger amounts spread into the upper reaches of the epidural space. Although individuals vary, averages serve as a valuable guide to dosage.

Speed of injection is a less dependable method of control. In general, a given amount of solution will produce effects at higher levels if it be rapidly injected. For perineal analgesia, for example, administration is slow, so that the greater part of the solution will remain at a low level and thus effect an economy of drug. Variation in size of the openings surrounding the nerve trunks at the sacral intervertebral foramina may influence speed of injection as a controlling factor, and may account for its lack of reliability.

The effect of gravity on solutions injected peridurally through the caudal canal is quite constant and is a valuable method for control of level of effect. By tilting the table down at the head, a given amount of anesthetic solution will produce effects two to three segments higher than when administered.

*Procaine 1.5 per cent in physiologic saline with epinephrine, pontocaine 0.2 or 0.25 per cent in physiologic saline with epinephrine, metycaine 1.5 per cent in physiologic saline with epinephrine.

†Some patients note tingling in the extremities during onset of analgesia with these drugs but this sensation is not usually unpleasant.

with the patient horizontal. Conversely, tilting the table down at the foot tends to puddle the solution at lower levels. The patient may be placed in the lateral position for unilateral operations as in inguinal hernia, the affected side being lower. By judicious combination of these methods one can produce varying levels of effect at will.

Control of depth of analgesia may be exercised through concentration of anesthetic solution. For all ordinary surgical and therapeutic caudal blocks, however, 1.5 per cent metycaine should be used. Control of duration of analgesia is exercised by administration of supplementary doses of drug solution at intervals determined by experience.

For the purpose of determining dosage and control methods required for satisfactory analgesia in a given case, we have found it convenient to make three categories, namely, low, mid, and high caudal block.

The term *low caudal block* is used when analgesia is required no higher than the 1st lumbar segment. It is used for operations upon the rectum, the perineum, as in perineal prostatectomy, vaginal plastic operations, including vaginal hysterectomy, and intra-urethral operations. It may also be employed for circumcision, excision of hydrocele and other procedures in this region if desired. For these operations it is necessary to completely block conduction in the 1st lumbar segment. When this is done, some disturbance of conduction (loss of sensation of pain) results at slightly higher levels. As most of the nerves which innervate these operative fields are near the sacral canal they are readily blocked with comparatively small amounts of solution.

For low caudal block an initial dose of 30 cc of 1.5 per cent metycaine solution is administered. This is given slowly and the table need not be tilted. Within 15 minutes this will produce surgical analgesia which will persist for about one hour. If subsequent injections are required, 30 cc at hourly intervals will suffice.

In certain instances low caudal block may be continued postoperatively. After hemorrhoidectomy 10 cc of 1.5 per cent metycaine solution may be administered hourly for 12 to 14 hours, with complete relief of pain during the period of block. Subsequent pain in the operative site has seemed less severe.

Mid-caudal block is employed for operations in which complete conduction block is required in the upper lumbar and lower thoracic segments as well as in the segments below. It is used for operations on the pelvic organs transperitoneally, suprapubic prostatectomy, inguinal and femoral hernioplasty, cesarean section, and, with a variation in technic, for operations on the lower extremities. In a previous report we could not recommend caudal analgesia for operative procedures requiring surgical analgesia above the umbilicus, but additional experience has convinced us that mid-caudal block is also useful for appendectomy and ventral hernioplasty.

For abdominal operations it is necessary to block the upper lumbar and lower thoracic nerves. Here again the trunks are comparatively small and traverse a short distance to the abdominal structures. They are readily

anesthetized by small amounts of solution per nerve. Therefore, in order to spread anesthetic solution into these upper levels the table is tilted down by the head at the time of injection.

This technic applied for low abdominal operations gives a safe, adequate anesthetic with good muscular relaxation. The patient remains in excellent condition throughout. In critically ill patients, operations may be performed with exposure and relaxation associated with spinal but with shock-free features associated with local. In cesarean section the baby is born ready to breathe and uterine tone usually will be found satisfactory without the routine use of oxytocics. In some instances it is necessary to make haste in removing the fetus and placenta in order to avoid technical difficulties from increased uterine tone. In cesarean section and with patients who are to be delivered of a massive ovarian tumor, it is wise to allow the analgesia to maintain its full height for 15 to 20 minutes before beginning operation.

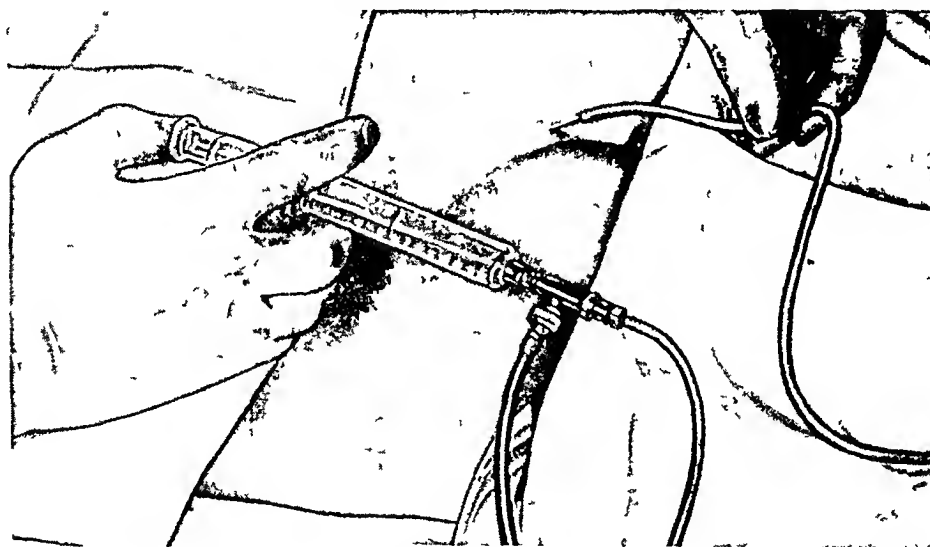


FIG 6—Special tubing attached over the collar of caudal needle illustrating use of continuous caudal apparatus

In mid-caudal block used for operations on the lower extremities it is desirable to concentrate a considerable quantity of anesthetic solution in the lumbar area so the lumbosacral plexus roots will be bathed in large amounts of drug. Because of their large size, increased amounts of drug solution per nerve are required to quickly and completely interrupt conduction. It is less important to affect the lower thoracic roots for analgesia of the extremities. Therefore, in order to concentrate effect in the lumbar region, the table is tilted down at the foot at the time of injection.

Mid-caudal block applied to operations on the lower extremities gives safe surgical analgesia with muscular relaxation which facilitates operative work. Such relaxation together with surgical analgesia may be obtained in the aged, or in recently shocked or debilitated patients, with a minimum of risk. We have found this anesthesia to be particularly suited for operative procedures upon the hip in the aged. Prolongation of operative time caused by roent-

CAUDAL ANALGESIA IN SURGERY

Form #M 28

No. 117378

ANESTHESIA RECORD
U. S. Marine Hospital
Stapleton, S.I., N. Y.

Date 7-21-43

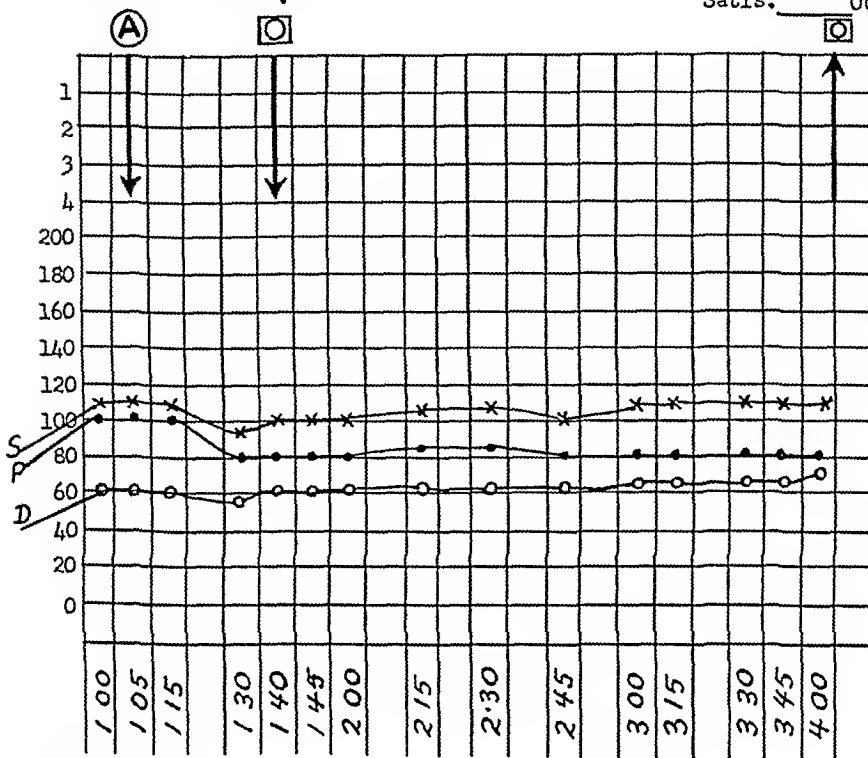
Ward B-4

Risk E G F (P)

Name Noonan Herbert Age 30

Premedication M5 gr 1/6 @ 1230

INDUCTION
Exc. NE Cough
Sev Laryn. Slow
Satis. Others



MAINTENANCE
Metycaine 1 1/2%
1.30 @ 105
2.30 @ 110
3.30 @ 115
4.50 @ 220
5.50 @ 330
6
7
190 cc

Agents Ind. Maint.
Tech. Ind. Maintenance
Operations Exploratory of the Biliary tracts (Drainage of hepatic duct - T tube)
Surgeons Ferguson-Southworth Anesth. Southworth
Johnson

POSITION RECOVERY CAUDAL
Sup Prone Trend M S Reflex in O.R. Yes No
Lith Trend M S Rotch Vomt
Fowler M S Lat Rest Excit M S
Tourn Others

Plasma 500 cc

enologic examination of internal fixation devices is not injurious. In obligate amputations upon patients with gangrene of arteriosclerotic or diabetic origin one may operate secure in the knowledge that the anesthesia adds nothing to the odds against the patient.

This type of anesthesia has been found of value in treatment of casualties injured below the umbilicus, as in compound fracture of the lower extremity. It has been found practicable to anesthetize these patients in the receiving room and conduct all subsequent examinations and treatment covering four- to six-hour periods, with the patient free from all pain. Prolonged anesthesia by means of continuous caudal block, plus an transport, might prove of value in treatment of certain battle injuries. For a surgeon experienced in the method this anesthetic is ideal for operations that must be performed in ships on the high sea, particularly when skilled assistance is not available.

For mid-caudal block an initial dose of 30 cc of recommended solution is

administered Five minutes is allowed to elapse and the sacral area is tested with a needle If saddle analgesia can be demonstrated the needle is situated within the sacral canal Five minutes after administration of the first 30 cc a second unit of 30 cc is administered and the anesthetic or operating table is tilted If the proposed operation is in the extremities the table is tilted down by the foot five degrees in order to hold the solution in the lumbar areas If the operation is in the pelvis or abdomen, the table is tilted down by the head five degrees in order to extend the effects more completely into the midthoracic area Twenty to thirty minutes after administration of the first unit of the dose, analgesia will be found complete With the technic recommended for abdominal work, surgical analgesia will extend to the costal margin Analgesia will persist for one to one and one-half hours Subsequent injections of 40 cc are given as required In pelvic operations the five-degree tilt of the table is maintained and is found to be sufficient to keep the bowel out of the pelvis While steeper angles are not contraindicated for anesthetic reasons, they will not be found necessary, and if not employed relieve the patient of the added burden of the weight of the abdominal contents against the diaphragm

When analgesia is required for operations in the upper abdomen and lower chest, that is, with complete conduction block to T4 or higher, we term the procedure *high caudal block* Our experience in this field has been limited to 33 cases, but the results so far have been encouraging Height of effect is achieved by use of increased volume of solution and by utilizing the effect of gravity Chart 1 is the record of a seriously ill patient operated upon under high caudal block, and returned to the ward in as good condition as when he left

For high caudal block an initial dose of 30 cc of recommended solution is given After five minutes the table is tilted down by the head five degrees, and a second 30 cc is given At the end of a second five-minute period a third unit of 30 cc is administered This procedure usually results in surgical analgesia to the nipples or clavicles thirty minutes after the first injection The effect persists for one to one and one-half hours Supplementary doses of 50 cc are given if required Table II summarizes in brief form the doses of anesthetic solution required for surgical procedures

TABLE II
SUMMARY OF DOSES RECOMMENDED
(Metycaine 1.5 Per Cent)

Type	Amt. Cc
Low caudal block	30
Mid caudal block	30-30
High caudal block	30-30-30

Intervals represented by dashes between units of initial dose are five minutes Supplementary doses are 30, 40, and 50 cc respectively

Certain technical details of importance in care of patients and in administration of continuous caudal analgesia have become apparent These include preoperative care, choice of instrument and technic of insertion, including precautions, and postoperative care

Caudal analgesia in surgery requires no change in routine of preoperative care, yet sometimes advantageous changes can be made. When the surgical condition permits, as in the case of vaginal plastic procedures, little immediate preparation need be given. The patient may be given a light breakfast, sent to the operating room without premedication, operated upon, and returned to the ward with little disturbance of the normal routine of living. Insulin and diet may be given as usual to diabetics. In the aged undergoing operation for painful conditions, preoperative medication should be omitted. Restlessness from disorientation, if present, may then be safely controlled with minimal doses of pentothal sodium. Patients who are to undergo cesarean section should have no preoperative medication.

For surgical procedures caudal block is started with the patient in the prone position. The hips may be elevated with a pillow. After the first unit of the initial injection the patient is turned to the position required by the surgeon. For cesarean section it is begun with the patient in the lateral position, as for spinal, but the patient is placed on her back before the second unit of the initial dose is given. A final inspection of the needle and its attachments should be made prior to draping in order to make certain that the needle is still correctly placed and that the conducting tubing is attached.

Since the introduction of continuous caudal analgesia, we have used a special malleable No. 19-gauge steel needle, devised by one of us (R. A. H.), which is allowed to remain in the sacral canal throughout the procedure. In our experience this has been the instrument of choice for the continuous technic. It is small enough to permit repeated trials at insertion with little trauma, a factor which is of importance to beginners. Flexibility of the needle allows it to assume the natural curve of the sacral canal while its comparative rigidity adds to the security of its position. Its small size minimizes entrance of infection when the apparatus is left in place for prolonged periods. After insertion of the needle the anesthetic solution is introduced in intermittent doses in amounts sufficient to maintain the desired effect.

Other instruments are in use. Adams, Lundy, and Seldon⁸ advocate use of a No. 13-gauge needle for original caudal puncture. Through this needle a No. 5 catheter is inserted. The needle is then withdrawn and the catheter is allowed to remain in the sacral canal. Irving, Lippincott, and Meyer,⁴ and Seiver and Mousel⁵ have also employed this technic, with slight modifications, with good results. In surgical patients we have found that insertion of a round-tip catheter well above the usual termination of the dura sometimes gives more rapid onset of analgesia in the abdomen. Block and Rochberg,⁹ and Posner and Buch,¹⁰ have advocated administration of anesthetic solution by means of continuous drip through a needle in the sacral canal.

Success obtained in the use of caudal analgesia depends primarily on the accuracy with which a needle can be inserted into the sacral canal through the sacral hiatus. This procedure is somewhat more difficult than lumbar subarachnoid tap, but one which can be readily learned. The technic has been well described^{11, 12}. For best results the needle is inserted with the bevel

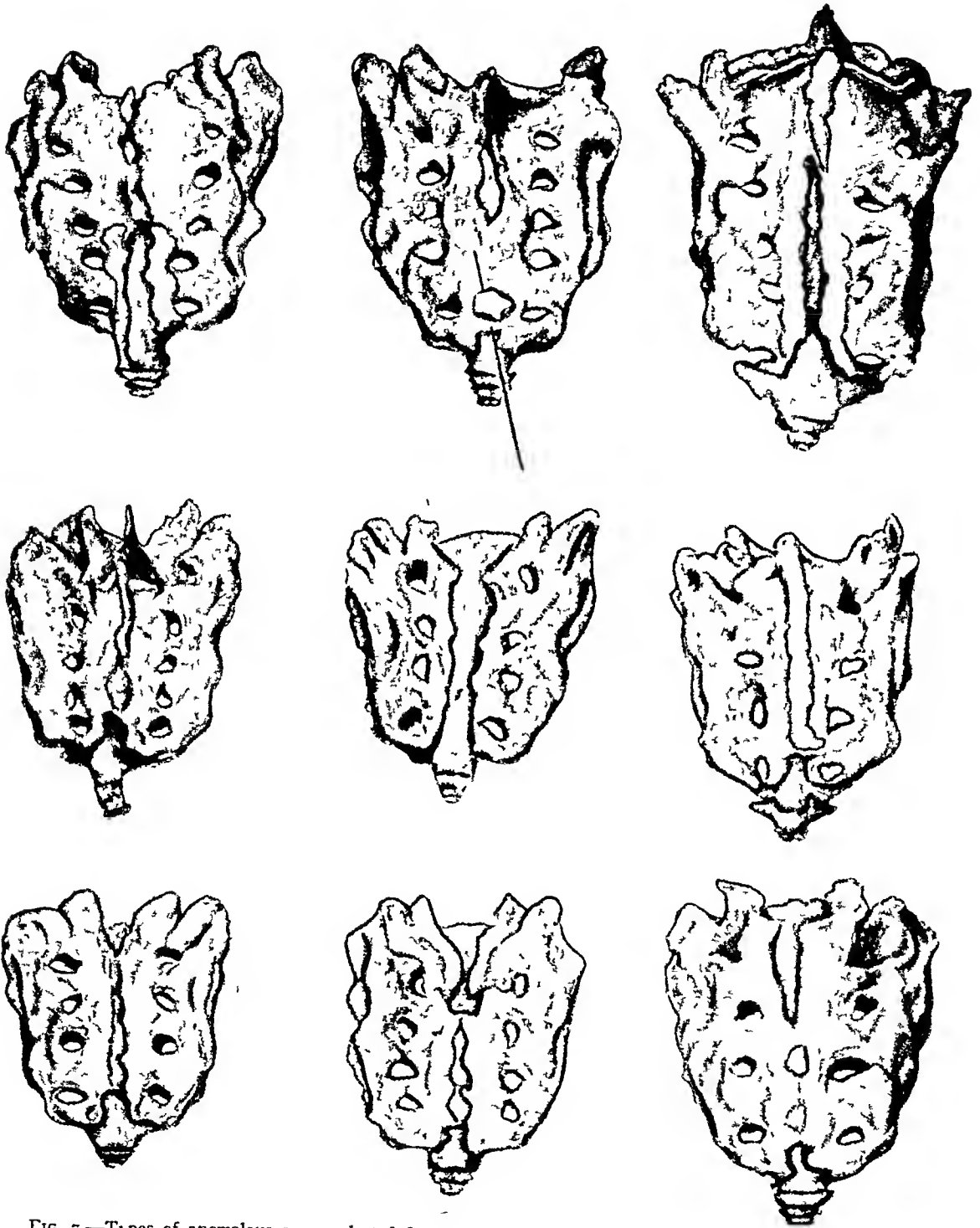


FIG 7—Types of anomalous sacra selected from 300 specimens from the Baugh Institute of Anatomy

posteriorly so that it will slide along the periosteum of the roof (posterior wall) of the sacral canal without piercing the periosteum or any of the thin-walled veins which are numerous in the lateral and anterior parts of the canal. For unilateral operations we have found it practicable to direct the needle to the affected side in order to produce quicker, more profound, unilateral analgesia. When done carefully, this has not been followed by increased incidence of bloody tap.

When using our technic several precautions must be taken. It is necessary to be sure that subarachnoid tap has not been performed inadvertently. In our experience careful aspiration will usually reveal cerebrospinal fluid if the dura has been pierced. Lundy¹³ recommends that aspiration be performed gently for more accurate results. We have performed inadvertent subarachnoid tap sixteen times in attempting caudal analgesia. In all but two instances clear or bloody spinal fluid flowed back freely into the aspirating syringe, anesthetic solution injected extradurally into the sacral canal cannot be freely aspirated. After subarachnoid tap, caudal analgesia should not be attempted in the same patient for 24 hours. Beginners or occasional operators, when using our technic, are advised to use a test dose of 8 cc of 1.5 per cent metycaine solution (about 120 mg) to be sure that occult subarachnoid tap has not occurred. This dose placed within the subarachnoid space in the sacral canal will produce a low, safe, spinal anesthesia in ten minutes, as evidenced by extensive saddle analgesia and definite motor weakness in the lower extremities. It will not produce a complete lower abdominal spinal anesthesia. If a low spinal is obtained from the test dose, no attempt should be made to extend the effects of the spinal by additional doses. Work done in this respect will be reported separately. If an 8 cc test dose produces no evidence of subarachnoid anesthesia, injection is carried on with doses recommended, the original 8 cc being disregarded.

The appearance of blood through the caudal needle does not necessarily constitute a contraindication to continuing the procedure. The needle is withdrawn a few centimeters, gently rotated, and reinserted. In this way free bleeding through the needle can be avoided. In robust patients undergoing elective procedures, injection may proceed immediately. In poor risk patients in the aged, and in patients who are to undergo cesarean section, ten minutes are allowed to elapse after bloody tap to allow clotting about the pierced vein. In this way one may avoid forcing significant amounts of anesthetic solution directly into the injured vein.

The postoperative course of patients operated upon under caudal block is smooth. Atelectasis, distention, urinary retention, vomiting, and phlebitis are rare. Motor paralysis rapidly wears away and the patient is able to move about in bed. Sensory block gradually fades leaving comparatively pain-free wounds. About one in twenty patients complain of soreness in the lower back but none have required special medication for relief, and it has not been noted by any on the second postoperative day. Headache as a sequela of the anesthetic has not been observed.

Caudal block may be employed for *therapeutic* purposes through its temporary paralytic action on the sympathetic system. Low caudal block from 30 cc of 1.5 per cent metycaine solution produces a lumbar sympathetic block that persists for about one hour. It may be employed in diagnosis and treatment of certain vascular diseases. Estimation of vasospastic factors in peripheral arterial disease in the lower extremity is facilitated by measurement of skin temperatures before and during temporary sympathetic paralysis.

The work of Leriche and Kunlin,¹⁴ and Ochsner and DeBakey,¹⁵ has shown that *acute thrombophlebitis* of the lower extremities is benefitted by a temporary block of the lumbar sympathetic system. Formerly this was done by lumbar paravertebral block. We have found that sympathetic paralysis may be produced by the simpler technic of caudal block. Low caudal block is sufficient to produce the desired result.

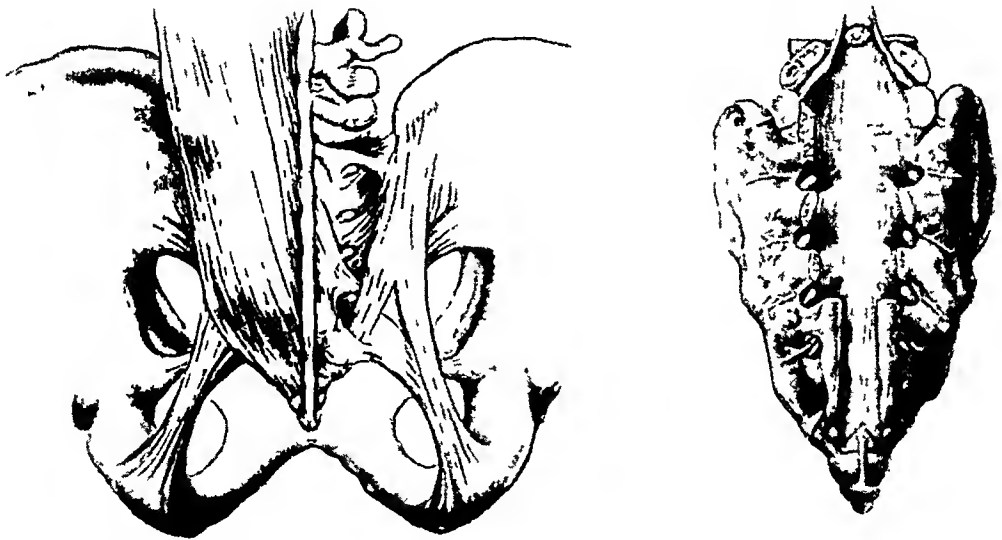


FIG 8—Posterior sacral ligaments and sacral canal with posterior surface of sacrum removed

This type of treatment for acute thrombophlebitis requires that a temporary lumbar sympathetic block be produced as soon as possible after the diagnosis is made and at frequent intervals thereafter until improvement or cure results. We have found an alternate method promising. A low caudal block is given and maintained for a period of four hours. It is then allowed to wear away for a four-hour period, but the needle is left in place. A second period of block is then begun and maintained for four hours, in all, a 12-hour procedure with eight hours of block.

Caudal block produces prompt, lasting pain relief in *phlebothrombosis* of the lower extremities and is a valuable adjunct in the treatment of this condition.

Epidural injections of saline or anesthetic solutions have long been used in treatment of *sciatica*. In the absence of organic changes in the adjacent structures or in the nervous system, that is, in idiopathic *sciatica*, some suc-

cess has been obtained. Kelman¹⁶ and others give massive dose injections with the purpose of releasing adhesions about the lumbar and sacral nerve roots. Evans¹⁷ is of the opinion that smaller doses are sufficient for this effect. We have considered the possibility that relief that occurs in idiopathic sciatica might be due to temporary interruption of pain and spasm, although it is difficult to correlate this view with the fact that occasionally small saline injections produce dramatic cures.

In the treatment of sciatica, a low caudal block is administered and the patient is asked to report his opinion as to the benefit he has derived after a lapse of 48 hours. If he feels that he is improved, a second and third treatment are given 48 hours apart. It is believed that maximum improvement is reached after three treatments. Empirically, we have treated 21 cases of sciatica of the idiopathic type with low caudal block, employing 1.5 per cent metycaine solution and have noted improvement sufficient to allow the patient to return to duty in fifteen cases.

Minor strains and contusions of the lower back are often benefitted by one or two low caudal blocks. It seems that in these conditions temporary relief of pain and muscle spasm is followed in some instances by prolonged relief of symptoms and cure. The patient is allowed to be judge of the efficacy of the treatment, and none are urged to undergo a second treatment if definite benefit has not occurred within 48 hours after the initial injection. Those who obtain prolonged relief readily submit to additional treatments even when they consider the treatment itself painful.

Intractable pain in the pelvic regions, when due to a temporary or surgically amenable lesion, may be relieved by continuous caudal analgesia. In this category perirectal cellulitis and abscess may be rendered painless in the preoperative stage. Perineal phlegmon, likewise, may be relieved if infection does not extend near the sacrum. Acute salpingitis sometimes responds favorably to repeated continuous caudal blocks with prolonged pain relief resulting. Localization of infectious processes is in no way interfered with by use of a continuous caudal block, in fact localization appears to be hastened. Pain from ureteral calculus may be relieved by caudal block. The analgesia may be administered for relief during a period of conservative therapy, preoperatively, or for operation. Occasionally, prolonged relief follows a metycaine caudal block in patients with pain from advanced pelvic carcinoma.

The observation that blood pressure may be restored to normal levels in hypertensive patients under the influence of caudal block brought up interesting possibilities. Southworth and Russek¹⁸ found that in all cases studied, blood pressure in the hypertensive is lowered, safely, for the duration of the block. A rapid return to previous levels occurs in fixed hypertensives. In some patients with labile blood pressure and intermittent hypertension, a period of temporary sympathetic paralysis as produced by caudal block is followed by comparatively prolonged levels (one to two weeks) of normal pressure, and by subjective improvement. It is not believed, however, that intermittent sympathetic block is of any value in treatment of hypertension.

Observations on a few patients with hypertensive crises have shown promise that some benefit may accrue from temporary lowering of arterial pressure.

Edwards and Hingson,¹ and Siever and Mousel,⁵ have observed beneficial effect from caudal block on eclamptic patients.

Continuous caudal analgesia has one definite *disadvantage* for routine use as a surgical anesthetic. It is time-consuming. When the services of a trained anesthetist are available so that cases may be prepared in advance, this factor is eliminated. As we gain more experience we find that the required time interval as described can be greatly shortened.

The *complications* of continuous caudal analgesia as applied in general surgery have been mentioned throughout the text but will be considered together here.

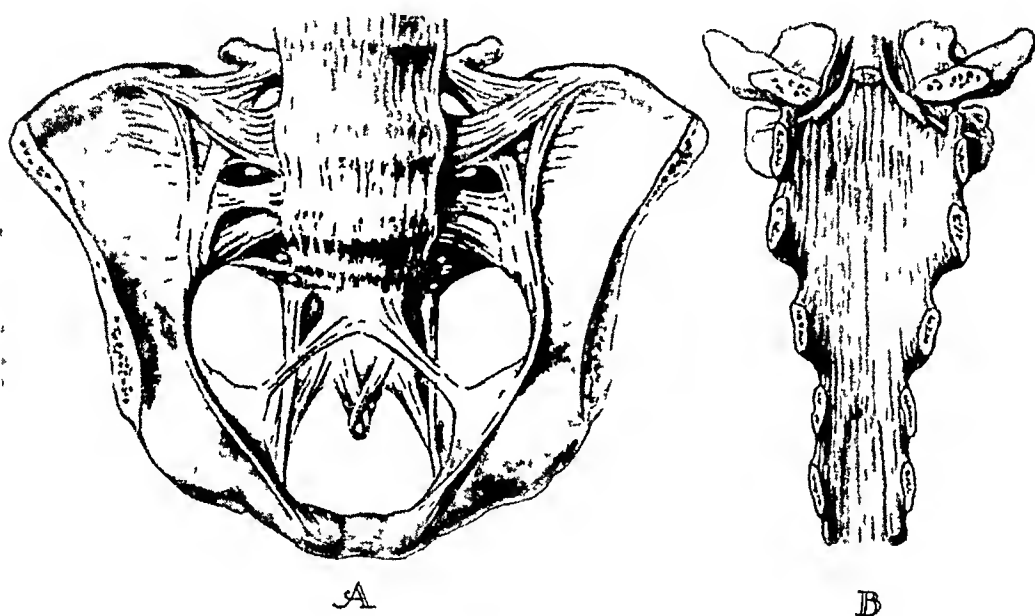


FIG 9.—Anterior sacral ligaments with roof of sacral canal exposed

Syncope has been observed in numerous patients during or shortly after the initial injection. This phenomenon consists of transient loss of consciousness for a few (10 to 30) seconds. In no instance has this been followed by any sequela whatsoever. The patient quickly regains consciousness and believes that he dozed off. It is thought that this minor complication is due to sudden compression of the dural sac. Dizziness and bradycardia, which occur at times during the course of an injection, may be due to the same cause.

Nervousness, nausea and occasionally vomiting may occur during the course of caudal analgesia. This is attributed to toxic effect of the anesthetic drug from rapid absorption. These symptoms may follow bloody tap in the sacral canal if sufficient time is not allowed for clotting to occur. Once we found it necessary to discontinue caudal analgesia because of bleeding and too rapid absorption of solution. Nausea and restlessness may be produced

CAUDAL ANALGESIA IN SURGERY

in sensitive individuals by sudden drop in blood pressure from a normal level. In some instances nausea may be caused through a more direct effect on the intestinal tract through its autonomic innervation. These symptoms have not occurred frequently in our experience.



FIG. 10—Anomalous sacrum with total failure of fusion of dorsal bony arches. This condition is present between 0.5 and 1.5% of cases.

Peripheral circulatory collapse from continuous caudal analgesia has occurred twice in our experience. In both instances it was due to the combination of too rapid onset of upper level analgesia together with too rapid absorption of anesthetic drug following a bloody tap. In one instance, for temporally elective cesarean section, it was thought wise to postpone the operation, although the circulation improved promptly after administration of ephedrine subcutaneously. In the second patient, an elderly diabetic undergoing elective hemioplasty, the operation was successfully undertaken after the blood

pressure and other symptoms had responded to the administration of $\frac{3}{8}$ gram ephedrine sulfate. No unfavorable sequelae followed either of these occurrences.

Infection has occurred twice as a complication of caudal analgesia in surgical patients. In one instance superficial cellulitis of low grade appeared about the needle entrance. No involvement of the sacral canal was present.

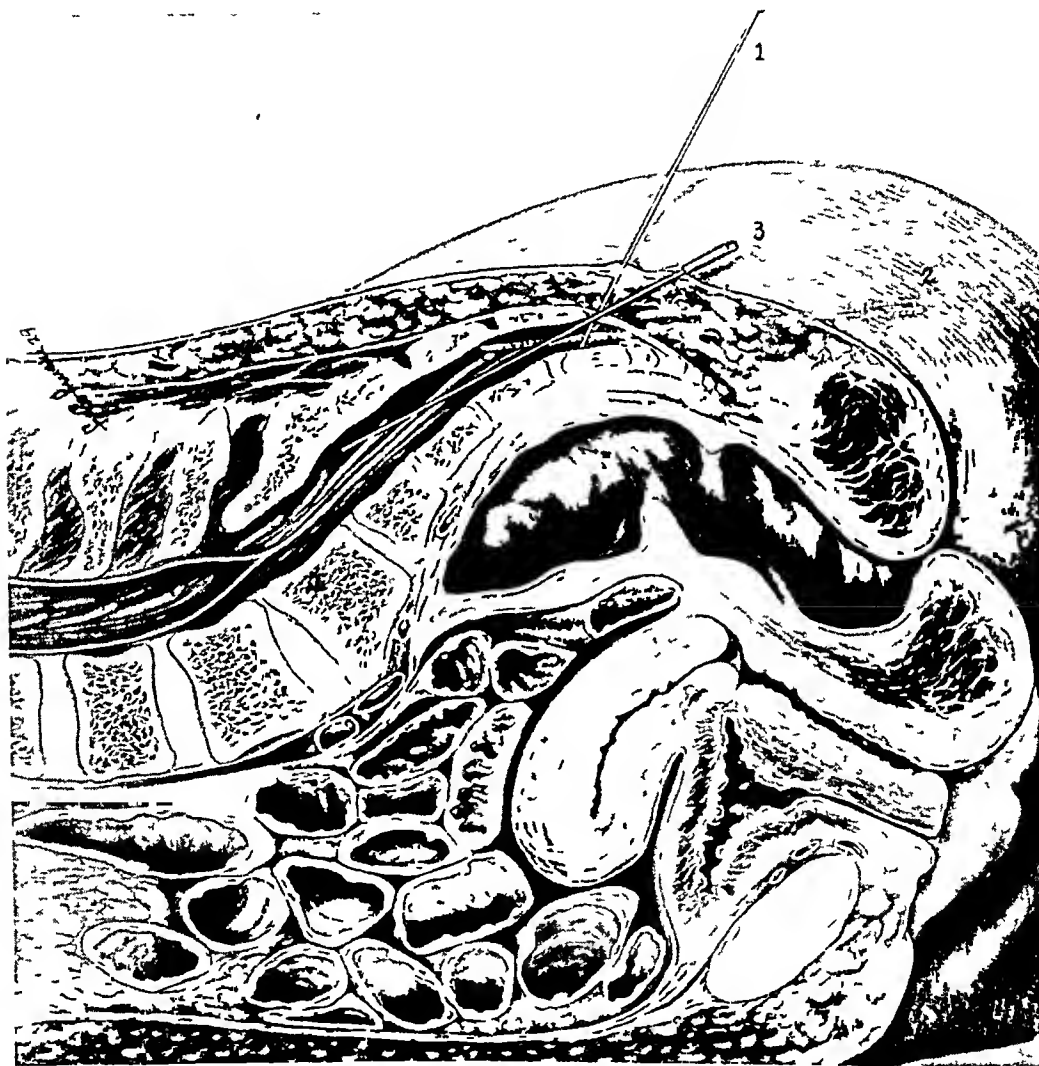


FIG 11—Showing special caudal needle in place in the sacral canal through sagittal section

and there was no nerve damage. This infection subsided after administration of sulfathiazole. In the second instance serous drainage from the needle site appeared. No involvement within the sacrum was present and this condition healed spontaneously. The possibility of infection is ever present in a continuous nerve block procedure. For this reason we now seal the junction of the skin and needle with a liberal amount of sulfathiazole ointment.

In our hands, continuous caudal analgesia has been 96.7 per cent effective for the operation for which it was intended. Failures have been due to learning, to teaching, and to anomalies of the sacrum. In two instances,

CAUDAL ANALGESIA IN SURGERY

with seemingly normal sacra and proper technic, we have been unable to raise the level of analgesia high enough for the procedure at hand. This occurred once in a patient with an inguinal hernia and once in a patient about to undergo abdominal perineal resection.

Continuous caudal analgesia in surgery may be supplemented by inhalation or intravenous anesthesia or additional local or regional block. It is not thought wise to employ spinal anesthesia directly after a failure at caudal. When it is desirable to supplement caudal for the patient's benefit, rather than for surgical or anesthetic reasons, sodium pentothal is the agent of choice. A small amount will keep the patient asleep.

TABLE III
LOW CAUDAL BLOCK
Anesthetic

Type	No
Perineal plastic operations	67
Transurethral operations	38
Hemorrhoidectomy	33
Miscellaneous urologic procedures	12
Miscellaneous gynecologic procedures	7
Manipulation of lower spine	6

Therapeutic

Thrombophlebitis	34
Diagnosis—vasospastic conditions	29
Treatment—vasospastic conditions	10
Sciatica	21
Miscellaneous	11
Low back strain	10

MID-CAUDAL BLOCK

Hernioplasty inguinal, ventral, and femoral	217
Operations on the pelvic organs transperitoneally	114
Cesarean section*	62
Phlebectomy and ligation of varicose veins	52
Open reduction, fractures of the lower extremity	47
Appendectomy	26
Arthrotomy of the knee joint	20
Open operation of the hip joint (in aged)	14
Amputation (major bones of lower extremity)	12
Skin grafting, plastic operations, below umbilicus	12
Miscellaneous procedures	8
Suprapubic cystotomy	8

HIGH CAUDAL BLOCK

Ventral hernioplasty (upper abdomen)	16
Miscellaneous operations involving upper abdomen	10
Cholecystectomy	5
Rib resection	1
Skin graft to upper scapular region	1

Total	903
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We have administered, or closely supervised, the administration of continuous caudal analgesia to 903 patients undergoing various surgical operations. The type and number of procedures are listed in Table III.

We conclude that continuous caudal analgesia is a useful addition to the

*Some of these cases will be reported separately by Dr. C. B. Lull.

Failures were as follows: Low caudal block, 3 or 1 per cent; mid-caudal block, 25 or 4 per cent; high caudal block, 2 or 6 per cent.

armamentarium of the surgeon and anesthetist, because it has the desirable features of regional and local anesthesia plus controllable duration and level of effect

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ADVANCES IN SPINAL ANESTHESIA*

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SEARCH FOR RELIEF OF PAIN has been the driving motive which has brought patients to doctors from time immemorial. It was not until means were developed whereby patients might be relieved from pain during surgical procedures that the real refinements of surgery began. Inhalation anesthetics were among the first to prove a great boon to patients and surgeons alike. Paradoxically, however, they had then harmful effects during operation and postoperatively because of the great stress upon the cardiorespiratory system.

Undoubtedly, many deaths have been directly due to inhalation anesthetics, most of them attributed to other causes, chiefly the disease and operation.

LOCAL ANESTHESIA Valuable as the inhalation anesthetics have been, there has been a constant study by anesthetists to find other means of relief from pain without the cardiorespiratory stress caused by these agents. The discovery of cocaine and its use was a big improvement in anesthesia. Noyes, of New York, was prompt to use it in 1884. However, cocaine had its dangers and limitations. These have been succeeded by the cocaine substitutes, some of which are more dangerous than cocaine.

Local and regional anesthesia undoubtedly are the safest anesthetics^{*} for use in surgery. However, there are certain patients who are not psychologically suited for any local anesthetic and certain long operations do not lend themselves readily to regional and local anesthesia.

SPINAL ANESTHESIA Corning, of New York, using what he termed as "Procedure in Therapy Which Possesses the Merit of Novelty," attempted to produce spinal anesthesia. In an article published in October, 1885, entitled "Spinal Anesthesia in Local Medication of the Cord" he said "As the introduction of a hypodermic needle beneath the membrane of the medulla spinalis is not practicable without the removal of the arches

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of the vertebrae (on account of the dangers of wounding the cord), I decided to inject the anesthetic between the spinous processes of the lower dorsal vertebrae. I was bent upon abolishing reflex action and annulling sensory conduction in the cord." Anesthesia of the legs and genitalia resulted, and a sound was passed painlessly through the urethra. Because cocaine in doses greater than one-half grain was too dangerous in general use, the method was not generally adopted and fifteen years were to pass before the surgical possibilities of spinal anesthesia were demonstrated clinically by Bier, of Kiel, in 1898. Quincke, in 1891, had demonstrated the utility of the lumbar puncture and showed that the introduction of the needle into the dura was feasible. So Bier, after experimenting upon animals and his own spinal canal, and his associate, Hildebrand, injected themselves with solutions of cocaine in 1898. The method was used so unwisely that Bier, in 1904, was called upon to sound a warning about its too extensive use. He realized some of the deleterious effects of cocaine and decided to wait for the discovery of some less toxic drug. In 1903, Fournier brought out *stovaine*, which became generally used throughout England and France. In 1904, Einhorn, in Germany, discovered *procaine* (*novocain*). In America, Adams discovered *butyn*, and Loevenhart and Schmitz brought forward *isocaine*. As the resultant development of these safer drugs, the use of spinal anesthesia has become general and widespread. Where it has been carefully used, the morbidity and mortality rate is below other types of anesthesia.

We believe it is responsible for lowering the mortality rate after prolonged operations such as those of resections of carcinomatous growths from the intestinal tract. We have used it with striking success for patients suffering with diseases requiring long operations at this hospital. One cannot but be impressed by the postoperative condition and course in poor-risk patients by the smooth recovery and convalescence which would not be looked for in ordinary circumstances following inhalation anesthesia. This is especially true in the use of continuous caudal and continuous spinal anesthetics which permits the use of a minimal amount of drug and, in the case of spinal anesthesia, partial withdrawal at the conclusion of the operation.

As time goes on, undoubtedly newer drugs and newer methods will continue to be introduced for the relief of pain for medical conditions and surgical procedures. We believe that the present use of spinal and caudal anesthesia is a big advance over former years.

For two decades spinal anesthesia has been one of the most satisfactory methods of rendering insensibility to pain in the surgical services of the United States Public Health Service Marine Hospitals. Since Pitkin's monumental work of repopularizing this method of anesthesia, with increased facility of administration and a wider margin of safety for the patient, spinal anesthesia has made its own place of popularity among both the surgeons and patients. Within the last five years spinal anesthesia has become the method of choice in 30 per cent of our operative cases. Since January 1, 1938, we

have performed 5,150 spinal anesthetics in the United States Marine Hospital at Stapleton, Staten Island, New York

It is our purpose in this paper to present our successful use of spinal anesthesia incidence of the complications, the indications and contra-indications of its use, the technic employed, the addition of present-day improvements and modifications in methods of administration, and a discussion of the types of drugs used for this procedure

We wish to present a modification of the apparatus for continuous spinal anesthesia designed by one of the authors

The types of patients that we have in the Marine Hospital are entirely different in many respects from those seen in the average civilian hospital. The great majority of them are robust males with well developed muscular frames, in the age-scale between 18 and 45 years. These patients, for the most part, live an active seafaring life with the Merchant Marine and Coast Guard.

We have found that spinal anesthesia, in a comparative study of 10,000 surgical operations done in our hospital, equals the safety of general anesthesia.

The likelihood of operating room deaths is no greater with spinal than with general anesthesia. With proper technic the likelihood of serious nerve and meningeal damage is infinitesimal. Most abdominal operations are greatly facilitated by this method. For certain ones it is almost impossible to operate without it.

In many operations extensive trauma under general anesthesia is inevitable. In such instances the risk of spinal, if any exists, is more than offset by the decreased risk resulting from the lessened visceral trauma made possible by the more complete relaxation.

We have found that the incidence of success with spinal anesthesia varies with the experience and skill of the anesthetist and the close cooperation of the surgeon in the choice of the anesthetic agent. For the purpose of analysis, we have divided our 5,150 spinal anesthetics into the following groups:

- 1 Spinal anesthesia for orthopedic operations upon the lower extremities
- 2 Spinal anesthesia for hernioplasty
- 3 Spinal anesthesia for rectal and lower urologic operations
- 4 Spinal anesthesia for intraperitoneal lower abdominal operations
- 5 Spinal anesthesia for upper abdominal operations

Table I presents the five-year summary of these cases in regard to types of operations performed, topographic zones of the operative fields, and the degree of success attained with each of the indicated agents. The term "intentionally combined" indicates those operations in which the spinal anesthesia was satisfactory, but which were supplemented by other general anesthetics, usually pentothal sodium, as a means of providing factors of safety, comfort, or of systemic therapy indicated by the condition and reaction of the patient. The term "necessarily combined" indicates a total or partial

TABLE I

FIVE-YEAR SUMMARY OF 5150 CASES IN WHICH A SPINAL ANESTHETIC WAS ADMINISTERED

	Urologic Rectal	Hermo- plasty	Lower Abdomen	Upper Abdomen	Lower Extremi- ties	Success ful	Inten- tionally Com- bined	Neces- sarily Com- bined	No of Cases
1938									
Spinocaine	300	237	35	6	2	582	2	3	585
Pontocaine	12	100	60	10	3	187	2	3	100
Metycaine	7	10	10			27			27
Nupercaine	9	9	20	10	2	50			50
1939									
Spinocaine	283	174	38	5		505	5	3	508
Pontocaine	10	120	65	8	3	208	2	3	211
Metycaine	2	1	1			4			4
Nupercaine	9	7	11	10	2	40	11	2	42
1940									
Spinocaine	304	7	13	2	3	329		3	332
Pontocaine	15	227	110	10	16	379	1	4	383
Metycaine	6	88	16	8	4	123	1	5	128
Nupercaine	4	5	17	9		27	2	3	30
1941									
Spinocaine	420	4	1			425			425
Pontocaine	7	174	100	32	4	327	10	13	430
Metycaine		2	1	2		5			5
Nupercaine		8	5	15		30	2	3	33
1942									
Spinocaine	461					461			461
Pontocaine	5	185	140	40	10	421	21	3	424
Metycaine		2	2	1	1	6			6
Nupercaine		1		1		1		1	2
Totals (first half 1943)	300	500	100	50	8	934	12	24	958
Totals	2155	1860	746	220	58	5077	71	73	5150

failure of the spinal anesthetic agent to give relief of pain and adequate relaxation

The agents used in this study were

1 Spinocaine, prepared by the method of Pitkin as a hypobaric solution. Two hundred milligrams of procaine hydrochloride was used as a maximum dose in this preparation. One hundred fifty milligrams was the dosage for abdominal operations in the average case. Seventy-two to 100 mg were used for the average dosage in urologic and rectal operations.

2 Pontocaine hydrochloride, prepared by Winthrop as an isobaric solution, was used as a 1 per cent solution in a 2 cc ampoule containing 20 mg.

3 Metycaine hydrochloride, prepared by Lilly as an isobaric solution, was used as a 1 per cent solution in 2 cc ampoules containing 200 mg.

4 Nupercaine hydrochloride, prepared by Ciba as a hypobaric solution, was used in a 1 to 1500 dilution in a 20 cc ampoule.

Table II presents our estimation of the comparative action of these different preparations.

It can readily be seen that spinocaine and metycaine are shorter acting than are pontocaine and nupercaine but at the same time they have a relatively lower toxicity.

Since most of the surgical operations such as bilateral hernioplasty, gastric resections, nephropexy, and colon surgery require an anesthesia that will last between one and two hours, and occasionally longer, we have found that pontocaine has been the most satisfactory single-dose spinal anesthesia. For the average size male patient, which comprised by far the greater number of cases in our series, we used a dose of 17 mg diluted with spinal fluid up to 3 to 3¼ cc injected between the first and second lumbar spines at the rate of ½ cc per second without barbotage.

For operations lasting longer than two hours we selected a 1 to 1500 dilution of nupercaine according to the Jones technic, *i e*, 15 cc injected over a five-minute period into the individual five feet six inches tall, with the addition of 1 cc for each inch in height above five feet six inches. The maximum dose was 20 cc of this dilution.

TABLE II
ESTIMATION OF COMPARATIVE ACTION OF VARIOUS SPINAL ANESTHETICS

Name of Drug	Anesthetic Efficiency	Time of Onset of Anesthesia	Duration of Single Dosage of Anesthetic	Relative Toxicity (Basis Procaine Unit is One)	Relative Potency of Unit Action
Spinocaine (containing procaine as active principle)	90 to 100%	3 to 10 mins	30 to 80 mins	1	1
Metycaine	90 to 100%	3 to 10 mins	40 to 90 mins	1.25	1.25
Pontocaine	85 to 95%	6 to 15 mins	60 to 150 mins	8	10
Nupercaine	80 to 90%	15 to 30 mins	90 to 200 mins	20	15

Since 1942, we have almost replaced the use of nupercaine by substituting the safer and more easily controlled method of continuous spinal anesthesia, as devised by Lemmon. Our modification of Lemmon's technic has been that we have used metycaine in preference to procaine. We have also modified the Lemmon apparatus as illustrated in Figure 1. Our apparatus contains

- 1 A 20 cc Luer-Lok syringe
- 2 A cut-off valve
- 3 Three feet of 2 mm white rubber garter tubing
- 4 A special hubless spinal needle of malleable stainless steel
- 5 A special spinal anesthesia introducer
- 6 A No. 22-gage, two and one-half-inch fascia needle
- 7 A No. 24-gage, three-quarter-inch hypodermic needle

This spinal stainless steel needle* (4) is the same that we have devised for continuous caudal analgesia. Instead of a heavy metallic hub it has a reinforced three-quarter-inch steel collar. One-sixteenth of an inch from the solder reinforcement with the shaft of the collar is a special safety bead to prevent breakage. The needle is No. 19-gage, has a short bevel, with an extra outlet aperture near its point. The needle is so annealed that the proximal inch is of stiff steel, the middle one and one-half inch a malleable stainless steel, and the distal one-half inch is also of stiff or rigid steel.

* This needle is manufactured by the Becton, Dickinson and Co., of Rutherford, N. J.

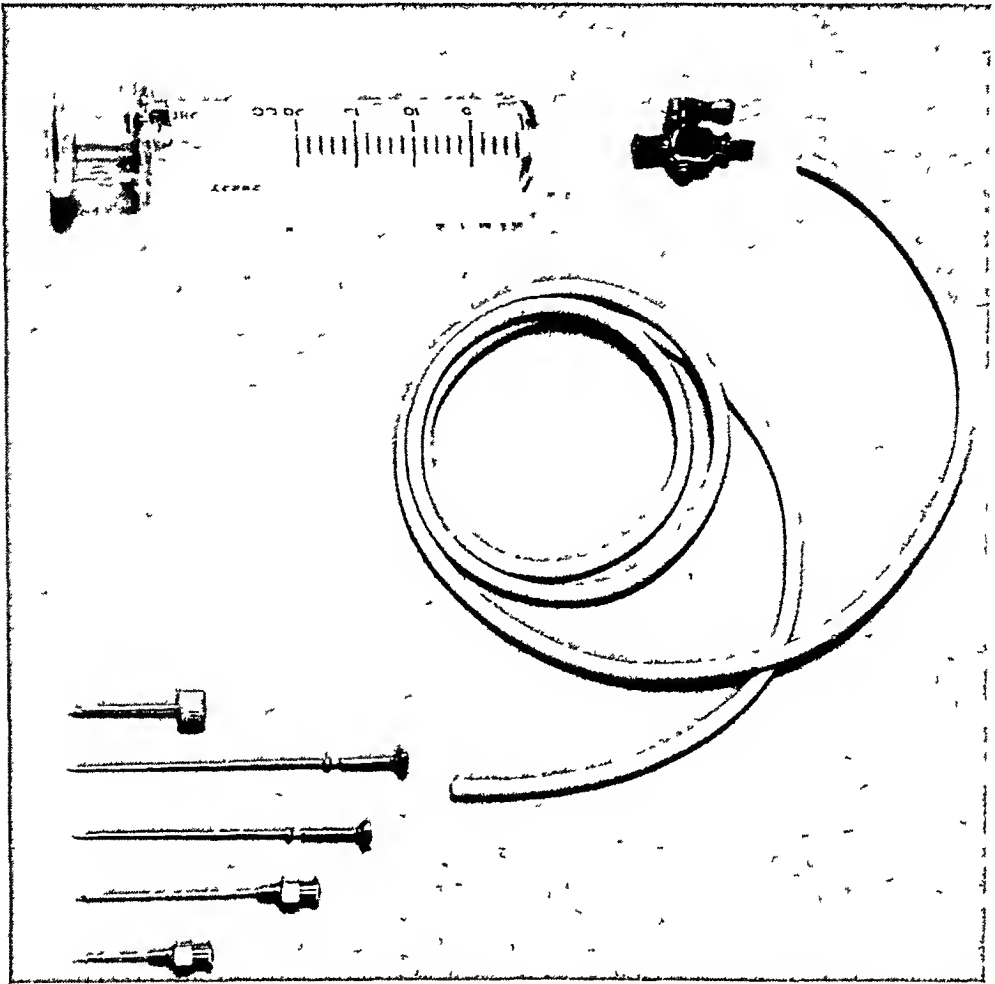


FIG 1—Continuous modified spinal anesthesia apparatus (B D) as used at the U S Marine Hospital, Stapleton, S I

The advantages of this needle obviously are

- 1 It is smaller, causing less trauma in introducing it into the sub-arachnoid space
- 2 The relatively heavy hub necessitating a still heavier Luer-Lok connector is replaced by a light collar over which is easily and securely slipped the garter tubing
- 3 The safety bead near the collar is to prevent breakage of the needle
- 4 Stiff or rigid proximal and distal portions of the needle maintain optimum position of the entire shaft relative to the skin, interspinous ligament and dura mater
- 5 A malleable center shaft allows mobility of the patient in transposing himself from the lateral or sitting posture to the dorsal recumbent one

We have found that this needle maintains its position during the operation more easily than the type usually recommended

Our technic of introducing the needle is the same as that recommended by Lemmon

We place 600 mg of 20 per cent metycaine, or 3 cc from the No 313 ampoule, in the 20 cc syringe After a free flow of spinal fluid has been

obtained, the special garter tubing is slipped with the collar over the needle shaft and spinal fluid aspirated gently into the syringe to the 12 cc mark. This makes a dilution of 5 per cent metycaine which should be thoroughly mixed by agitating the syringe. Each cubic centimeter then contains 50 mg of metycaine. The 2 cc of spinal fluid between the needle and syringe is then reinjected and an initial dose of usually 100 mg, or 2 cc of metycaine, is injected into the patient, with gentle barbotage.

The state of spinal anesthesia is maintained by serial injection of the drug as the patient requires it. The average abdominal operation usually takes 50 mg every 40 to 60 minutes. Contrary to the usual belief that all of the spinal anesthetic is neurogenically fixed in 20 minutes, we have been

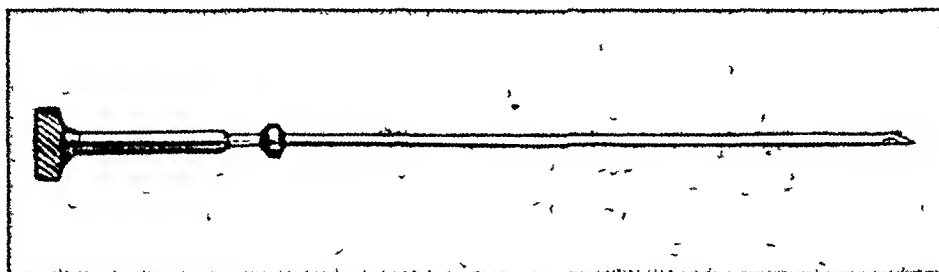


FIG 2—Improved caudal and continuous spinal needle (B D) described in text

able to withdraw from 7 to 20 per cent of the total anesthetic injected over the entire operation in 10 cc of spinal fluid after the surgery has been completed.

Table III presents data obtained from chemical assay of the metycaine withdrawn in a representative series of cases selected from a study of 50 spinal fluids.

Most of the patients from whom the unused or unneeded metycaine was withdrawn from the subarachnoid space promptly regained motor activity in the lower extremities in 5 to 20 minutes afterwards. There were no postoperative headaches or complications in the above series.

COMPLICATIONS IN THE TOTAL SERIES OF 5,150 CASES

I SPINAL DEATHS

There were two spinal deaths in this series. One occurred in an elderly male, age 72, who was given 16 mg of procaine for an amputation of a gangrenous leg. He died within three minutes after he was turned on his back without responding to resuscitation measures of vasopressor substances and oxygen inhalation with the gas machine.

The second of these deaths occurred in a robust coast guardsman, age 32 who had been given 130 mg of metycaine between the second and third lumbar spines for an hernioplasty. He suddenly developed a respiratory paralysis, progressive anoxemia and a cardiac failure beginning 12 minutes after the injection of the single-dose spinal anesthetic. Intratracheal intubation was quickly performed and artificial respiration by gas machine with 100 per cent oxygen was given for 11 minutes. Coramine and intravenous

TABLE III

DATA OBTAINED FROM CHEMICAL ASSAY OF METYCAINE WITHDRAWN POSTOPERATIVELY

(Gamma 02-methyl piperidino -propyl benzoate hydrochloride Lilly)

Samples from U S Marine Hospital New York

Name	Sample No	Date	Other Markings	Metycaine Found (Gm in Sample)
Pigut Anthony	1		114977	0 4153
Pigut Anthony	2		114977	0 0196
Rubes Anthony	1	5-3-43	114615	0 192
Rubes, Anthony	2	5-3-43	114615	0 0136
Daly Jos	1	4-14-43	112987	0 0785
Daly Jos	2	4-14-43	112987	0 0124
Winslow Wm	1	4-28-43	114293	0 280
Rodriquez Ramon	1	3-24-43	111034	0 071
Rodriquez Ramon	2	3-24-43	111034	0 0154
Olson Peter	1	4-28-43	114390	0 396
Olson Peter	2	4-28-43	114390	0 0226
Pontza V	1	3-22	112970	0 0259
Pontza V	2	3-22	112970	0 065
Fries Jr	1	3-29	112454	0 291
Fries Jr	2	3-29	112454	0 024
Burton Sally	1	3-5	109371	0 143
Burton, Sally	2	3-5	109371	0 006
Hyer Henry	1	4-7-43	113381	0 574
Hyer Henry	2	4-7-43	113381	0 096
Hoffman Carl	1	3-15-43	112675	0 353
Hoffman Carl	2	3-15-43	112675	0 062
Ovis B	1	3-18-43	111686	0 107
Kimble James	1	2-25-43	110993	0 164
Jaches Jack		7-29	118308	0 007*
Murphy, Peter		7-29	118304	0 00*

*Spinal fluid for control

The patients in the above series are representative ones taken from a study of 50 spinal fluids. Six hundred milligrams of 5% metycaine was used in each syringe for all of these cases.

Sample No. 1 contained the unused metycaine in the syringe and rubber tubing after the operation. Sample No. 2 contained the metycaine withdrawn in 10 cc of spinal fluid after the operation—indicating that a considerable quantity of metycaine remains in the spinal fluid for at least one hour after the initial injection.

ephedrine produced no response. As a last resort, one-half cubic centimeter of 1 to 1,000 adrenalin was injected into the heart.

After ten minutes with no cardiac function, as determined by clinical means, the patient suddenly developed a return to normal cardiac function, with a blood pressure return to preanesthetic 120/80 mm of mercury. The operation was not performed and the patient was returned to his bed. Cardiac and respiratory function appeared normal but the patient never regained consciousness nor the use of any muscles innervated by the spinal nerves. The patient died on the fourth postanesthetic day, with a temperature of 41° C. Autopsy revealed anoxemia, and degeneration of both cortical and spinal cord nerve tissues. There was present around the origin of the spinal nerves 17 cartilaginous tumors attached to the spinal cord. The pathologic nature of these tumors could not be determined in several laboratories.

II HIGH SPINAL ANESTHESIA

High spinal anesthesia and total spinal anesthesia occurred in 42 cases of the 5,150 injected. Twenty-five of these were successfully managed

with artificial respiration through the positive pressure gas machine and injection of a vasopressor introduced intravenously in those instances in which there was some collapse of the vasomotor system

The drug used for most cases was 25 mg of ephedrine sulphate. In a few of them intravenous glucose and saline, plasma, or whole blood was used to reestablish the vascular pressure.

In the remaining 27 cases there was ascending intercostal and finally diaphragmatic paralysis. In these cases a Magill intratracheal tube was promptly inserted with great facility because of the relaxation of the patient's lower jaw, larynx and vocal cords. One hundred per cent oxygen resuscitation was used until patient regained respiratory motor control.

The Trendelenburg position of about five degrees was used in the cases which appeared to have an ischemia of the respiratory center.

The onset of this complication is one that should be watched with constant diligence by the anesthetist. It should be promptly treated in the following order of precedence to the physiologic requirements of the patient:

1. Maintain oxygenation of the blood through prompt intubation or 100 per cent oxygen administered by artificial respiration with the gas machine.

2. Maintain blood pressure with vasopressor substances, such as 25 mg ephedrine or one-half cubic centimeter doses of 1 to 1,000 epinephrine injected intravenously.

3. Place patient in a five-degree Trendelenburg position for ischemia of the respiratory center in indicated cases.

4. Supplement circulating blood with intravenous administration of plasma, whole blood, and glucose and saline as indicated.

We have noticed in some of these high spinal anesthetics a sudden rise in systolic blood pressure to between 165 to 250 mm of mercury. If undetected, this temporary hypertension will suddenly and dramatically be replaced by total vascular failure.

III. NEUROLOGIC SEQUELAE

A. CRANIAL NERVE PALSY—Cranial nerve palsies have been reported in the literature as a relatively frequent complication of spinal anesthesia. In our series only one such instance occurred. The patient developed a complete paralysis of the right sixth cranial nerve 18 hours after a spinal anesthetic of 130 mg of metyamine. The paralysis has now persisted for a period of two years, with very little improvement. From the clinical signs, there must have been some degeneration of the abducens nucleus.

B. PERIPHERAL NERVE PALSY—Three of the patients have developed a foot-drop, with some motor weakness in both lower extremities following spinal anesthesia. Two of these patients recovered completely in two weeks, but one of them, after two years still has a motor weakness of the perineal muscles of the right leg. This patient was injected by an intern who produced con-

siderable trauma, with a bloody spinal fluid tap, in an attempt to insert the spinal needle

C HYERTHESIA AND HYPERALGESIA —In our series of 5,150 cases there have been 14 such cases, with diminished or painfully increased sensation of one or more nerve trunks. Most of these cases cleared spontaneously, but some of them required therapeutic regional nerve blocks with repeated novocain injections

IV HEMORRHAGIC MENINGITIS

This complication occurred in only one case, which required four attempts at lumbar puncture in order to produce a satisfactory anesthesia. For two weeks the patient had signs of clinical meningeal irritation with a leukocytosis of 14,000, and a high temperature. A therapeutic lumbar puncture was made and 15 cc of bloody spinal fluid was removed. The patient greatly improved after the withdrawal of the bacteriologically negative spinal fluid. There can be no question but that the trauma caused by the multiple punctures caused the hemorrhagic meningitis.

V HEADACHE

This complaint was mentioned to us by only one per cent of our patients. A few of them were completely relieved of the pain with ten grains of aspirin. However, six of our patients had persistent headache lasting two weeks, necessitating codeine and even morphine for relief.

VI MARKED FALL IN BLOOD PRESSURE

These falls in blood pressure occurred in individuals in whom the level of anesthetic was permitted to go higher than the eighth thoracic segment. Apparently the blood pressure fall had a direct relationship to the number of white ram communicantes that were blocked and the anesthetic efficiency of the drug.

Falls in blood pressure were successfully treated by one of the vaso-pressor substances, such as ephedrine, epinephrine or neosynephrin injected intramuscularly or intravenously, depending upon the needs of the patient. The Trendelenburg position of about five degrees was also useful in raising the pressure and delivering an adequate circulating volume to the brain and respiratory center. It is our plan to give a prophylactic injection of 25 mg of ephedrine sulphate into the muscle at the time of anesthesia to the debilitated patient. For the patient undergoing a major operation we gave a simultaneous prophylactic intravenous injection of five per cent glucose and saline, plasma, or whole blood during the course of the operation.

VII NAUSEA

Nausea on the operating table is generally caused by

(1) Sympathetic pain from manipulation or pulling of the visceral organs

(2) A rapidly falling blood pressure

(3) An increased peristalsis or some reverse action upon release of the parasympathetic vagal impulses with sympathetic block

Nausea may be combatted with blood pressure restorative measures when indicated, 100 per cent oxygen inhalations, and in severe cases (with adequate blood pressure) we used the administration of small quantities of intravenous sodium pentothal

VIII POSTOPERATIVE DISTENTION AND ATELECTASIS

This complication was seen as often, but in no greater incidence, than those cases associated with general inhalation anesthesia in our clinics

SUMMARY

The recent advances in spinal anesthesia, namely, (1) the principle of continuous spinal anesthesia, with an improved method of administration, (2) the addition of a more compatible supplement such as sodium pentothal, (3) more careful selection of cases for the procedure have greatly increased the benefits of this method for both the patient and the surgeon, (4) uniform results obtained with both long and short acting anesthetic agents in properly selected cases, and (5) partial withdrawal of unused and unfixed spinal anesthetics after operation permits more rapid return of physiologic nerve function

The incidence of success for this method varies directly with the skill and experience of the anesthetist. There must be recognized that a permanent hazard exists in the administration of this type of anesthesia. For our type of service, the advantages far outweigh the disadvantages, with the result that spinal anesthesia has become our most reliable method of surgical pain relief

FURTHER EXPERIENCES WITH ADRENAL CORTICAL EXTRACT IN THE TREATMENT OF BURN SHOCK

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IN 1941 Rhoads, Wolff, and Lee reported favorably on the use of adrenal cortical extract in conjunction with plasma in a group of seven burned patients. As this series was too small for satisfactory evaluation of the extract the study was continued until 1943. The results in this larger series have not fulfilled the promise of the earlier cases. They do not provide a satisfactory basis for the use of adrenal cortical extract in the routine treatment of shock following burns.

The patients for the study were selected from a group of fifty-three admitted to seven Philadelphia Hospitals between September, 1942, and January, 1943 (Table I). The criteria on which the selection was based are listed in Table II. A number of variations in the criteria were tried without significantly altering the results.

The clinical management of the cases could not be completely standardized but insofar as it was possible the time table in Table III was followed. The local treatment outlined is not necessarily recommended by the authors. In fact, we now prefer open methods. It was followed because it represented a standard form of practice when it was begun and because it was desirable to avoid changes in local treatment during the course of the study in order to maintain it as a constant factor.

The plasma volume and total plasma proteins were calculated from serial determinations of the hematocrit and the plasma protein concentration as described in previous communications from the Pennsylvania Hospital^{1, 2, 3}

In order to compare the results obtained in patients with burns of different extent and to average the results obtained in babies and large adults without greater weight to the larger individuals than the smaller ones the following plan was followed:

At about the twelfth hour after the occurrence of the burn, the plasma deficit was calculated. Approximately this amount of plasma was then administered between the twelfth and thirtieth hour after the burn. The plasma deficit at the thirty-sixth hour was then calculated and the net increment in the circulating plasma between the twelfth and thirty-sixth hour was compared with the amount of plasma administered. Thus, if the net increment was 500 cc and 1000 cc had been transfused, 50% of the transfused plasma was considered to have been retained.

* The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Pennsylvania Hospital.

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ADRENAL CORTEX IN BURN SHOCK

TABLE I

Name	Age	Sex	Referring Hospital	Area of Burn (Per Cent)	Local Treatment	Adrenal Extract	Hematocrit Rise
M A R	6	F	Germantown	10	Tannic acid	Eschatin	14
F H	40	M	Phila Gen	40	Tannic acid	Eschatin	29
L M	13	M	Germantown	20	Tannic acid	Upjohns	20
H M	27	M	Univ of Pa	16	Tannic & gentian		6
L W	22	M	Pennsylvania	22	Gentian & silver		16
I M W	1	F	Pennsylvania	35	Gentian & silver		20
E F	3	F	Univ of Pa	35	Gentian & silver		20
R L	20	F	Pennsylvania	10	Gentian & silver		6
R L	5	M	Germantown	10	Triple dye		9
O B	17	M	Univ of Pa	40	Tannic & gentian		12
R T	22	F	Pennsylvania	5	Gentian & silver		3
R B	42	M	Graduate	20	Open R		20
R J	18	M	Univ of Pa	5	Tannic acid		5
J K	1	M	Pennsylvania	7	Gentian & silver		5
P A F	1	F	Childrens	5	Gentian & silver		8
R B	6	M	Germantown	15	Triple dye		22
W G	40	M	Pennsylvania	10	Open R		10
M M	77	F	Pennsylvania	80	Gentian & silver	Eschatin	8
E J	30	F	Pennsylvania	7	Open R		10
M A	28	F	Univ of Pa	80	None		35
N B	25	M	Univ of Pa	8	Pickerell sol		5
W F	46	M	Pennsylvania	4	Soda bicarb		5
H G	63	M	Pennsylvania	15	Open R	Eschatin	4
R A	64	F	Pennsylvania	90	Gentian & silver	Kendall	18
T K	39	M	Germantown	90	Triple dye	Eschatin	25
J M	60	F	Pennsylvania	12	Open R	Eschatin	10
N C	6	F	Childrens	11	Gentian & silver	Kendall	10
J M	9	M	Graduate	10	Gentian & silver	Kendall	4
A V A	46	M	Pennsylvania	10	Gentian & silver	Kendall	2
J D	6	M	Univ of Pa	10	Tannic & gentian	Kendall	9
C S	10 mos	F	Childrens	8	Gentian & silver	Kendall	7
F R	51	M	Pennsylvania	12	Gentian & silver	Kendall	9
M K	19	F	Germantown	90	Tannic acid	Eschatin	22
J S	45	M	Germantown	12	Gentian & silver		14
C B	2	M	Univ of Pa	16	Tannic acid		11
L H	66	F	Graduate	50	Gentian & silver	Eschatin	17
B A	35	M	Graduate	16	Gentian & silver	Kendall	11
A W	38	M	Germantown	30	Triple dye	Eschatin	10
F H	35	M	Pennsylvania	10	Open R	Eschatin	5
P G	55	M	Germantown	45	Triple dye		20
W S	38	M	Pennsylvania	12	Gentian & silver	Kendall	10
G M	8	F	Graduate	20	Gentian & silver	Kendall	11
M R	6	F	Childrens	12	Gentian & silver		9
R G	9	M	Childrens	12	Open R		3
J A	60	M	Pennsylvania	8	Open R		5
G S	16	F	Pennsylvania	7	Gentian & silver		9
J P	4	M	Germantown	12	Pickerell sol		11
J B	34	M	Germantown	5	Triple dye		2
D C	5	M	Pennsylvania	7	Open & press		10
W S	18 mos	M	Pennsylvania	10	Gentian & silver		8
J G	23	M	Mercy	20	Gentian & silver		14
M R	22	F	Pennsylvania	8	Gentian & silver		11
C A	21	M	Pennsylvania	5	Gentian & silver		3

TABLE II

Patients were selected for the study from Table I if they fulfilled the following criteria

- 1 At least 8% of body surface burned
- 2 At least an eight-point rise in the hematocrit (In some instances the normal had to be estimated from the value at which the hematocrit levelled off on the 3rd and 4th days)
- 3 Local treatment by a tanning method except for hands and face and genitalia
- 4 Plasma transfusion between the 12th and 30th hour after the burn amounting to at least two-thirds of the estimated plasma deficit

TABLE III

DIRECTIONS USED FOR THE ROUTINE TREATMENT OF PATIENTS HOSPITALIZED FOR BURNS

IMMEDIATE

- 1 Draw 6 cc of blood in a heparin tube
- 2 Give morphine sulfate gr $\frac{1}{4}$ (h) (this dose for adults only)
- 3 If in shock start a 500 cc plasma infusion

AS SOON AS CONDITION PERMITS

- 1 Cut clothes away from burn
 - 2 Lift on to litter covered with sterile sheets and blankets
 - 3 Move to operating room or special room for burns and débride (superficially) on the litter. Additional morphine gr $\frac{1}{4}$ is often needed. General anesthesia is to be avoided. Wash the area gently with white soap and sterile water—loose skin being peeled away. Then rinse with sterile saline solution.
 - 4 Start tanning at once
 - 5 Transfer to a sterile bed covered with a canopy for regulation of the temperature. Temperature should be adjusted to about 80° F.
 - 6 If plasma has not already been started, set up a continuous intravenous infusion of equal parts of plasma and 5% dextrose solution and allow it to run at the rate of 100 cc per hour for burns up to 15% of the body surface and 200 cc per hour for larger burns.
 - 7 Continue tanning at $\frac{1}{2}$ hr intervals until the surfaces are dry.
- 6th hour Take another 6 cc sample for hematocrit and plasma protein—adjust infusion to keep hematocrit below 55 or within 10 points of the original hematocrit (whichever is lower)
- 12th hour Obtain 3rd specimen
Calculate the plasma deficit estimating the patient's weight from the history and physical examination and regulate the infusion so as to give approximately this amount between the 12th and 30th hour
- 18th hour 4th specimen
- 24th hour 5th specimen
- 30th hour 6th specimen
- 36th hour 7th specimen Stop infusion if hematocrit is below 50
- 42nd hour 8th specimen
- 48th hour 9th specimen
- 3rd day 10th specimen
- 4th day 11th specimen

All specimens are used for the determination of hematocrit and plasma protein concentration, and van den Bergh, N P N, serum CO₂ and serum chloride are determined as indicated.

ADRENAL CORTEX ADMINISTRATION

The treated cases were given eschatin in doses of 10 cc intravenously every six hours or the "whole extract of the adrenal cortex" in doses of 10 cc every two hours intravenously. In a few instances it was necessary to give certain of the doses intramuscularly. In the case of children the dosage was reduced but it was never reduced more than in proportion to the weight.

The mean per cent retention for the treated series was 57% in terms of plasma volume as compared with 57% for the control series (Table IV). In terms of grams of circulating plasma protein the mean per cent retention for the treated series was 46% as compared with 57% for the control series (Table IV).

The control series and treated series are compared with respect to age and extent of burn (Table V). It was difficult to compare them with respect to the depth of the burns because of the uncertainties of estimating this factor. However, the incidence of scalds as opposed to flame burns was not very different in the two groups. (Two due to hot water in the treated

TABLE IV—A
CONTROL CASES

Name	Plasma Volume 12th Hr	Plasma Volume 36th Hr	Plasma Retained	Plasma Given	Per Cent Retained	Plasma Protein 12th Hr	Plasma Protein 36th Hr	Plasma Protein Retained	Plasma Protein Given	Per Cent Retained
M R	962 cc	1067 cc	105 cc	205	51	54.7 Gm	60.8	6.1	12.7	48
F R	2260	2790	530	990	54	145	180	35	61.5	57
J S	2890	3490	600	1080	56	206	242	36	67	54
E F	224	586	362	810	45	15.6	38.3	22.7	50	45
I W	161	279	118	250	47	9.2	15.7	6.5	15.5	42
R L	716	740	24	200	12	35.1	39.6	4.5	12.4	36
L W	1670	2710	1040	1300	80	104	162	58	80.5	72
O B	2220	3190	970	1850	52	133	190	57	115	50
H McC	3300	3960	660	1325	50	210	248	38	82	46
C B	440	648	208	200	104	24.3	38.0	13.7	12.5	109
M R	2105	3270	1165	1050	111	138	185	47	65.0	72
J G	1972	2630	658	1375	48.0	127	160	33	85	39
G S	550	686	136	440	31	30.7	34.8	4.1	27.3	15
Average					57.0%					52.7%

TABLE IV—B
TREATED WITH EXTRACT

Name	Plasma Volume 12th Hr	Plasma Volume 36th Hr	Plasma Retained	Plasma Given	Per Cent Retained	Plasma Protein 12th Hr	Plasma Protein 36th Hr	Plasma Protein Retained	Plasma Protein Given	Per Cent Retained
A W	700 cc	4260 cc	1560 cc	2100	74	173 Gm	236 Gm	63 Gm	130	48
M R	647	805	158	315	50	42	45.2	3.2	18.9	17
W S	650	3380	730	1380	53	177	217.	40	53.5	75
G M	660	880	220	565	39	389	545.0	15.6	35	45
B A	1990	2560	570	1400	41	126	145.5	19.5	87.	22
P G	1340	2250	910	2110	43	80.6	145	64.4	131	49
I H	800	2110	1310	1300	101	84.5	104	19.5	59*	33
L H	1440	1950	510	1440	35	94.8	142	47.2	89	53
I M	1060	1160	100	550	18	61.5	73.8	12.3	34	36
M K	1390	2580	1190	900	132	93.1	134	40.9	56	73
J D	668	816	148	250	59	43.6	51.4	7.8	15.5	50
N C	750	916	166	390	43	46.8	59.7	12.9	24.2	53
Average					57					46

*Protein calculations extend from 16 to 36 hours

group, and three due to hot water and one to hot creosote in the control group)

DISCUSSION—The studies of Elkinton, Wolff and Lee² indicated that the tendency for infused plasma protein to disappear from the circulation had largely abated after 40 hours. The period from the twelfth to the thirty-sixth hour was selected as being the period when adrenal cortical extract would be most likely to exert a demonstrable influence. In the earlier paper the period from the eighteenth to the forty-second hour was used. Recalculation of these data on the basis of the twelfth to thirty-sixth-hour interval showed that the seven treated patients in the earlier group

TABLE V

	Control	Received Adrenal Cortex
Average age	18 yrs	29 yrs
Average area of burn	21%	26.8%

retained 69% by volume and 57% by weight as compared with 57% by volume and 46% by weight for the present treated series.

Two adrenal cortical extracts were employed in the present study. The results obtained with the extract used in the earlier series averaged 62% retention in cubic centimeters as compared with 46% retention for patients treated with an extract especially rich in those steroids which are important in carbohydrate metabolism (furnished through the courtesy of Dr. E. C. Kendall). Calculated in grams the retention was about the same for the two extracts.

It was suggested that adrenal cortical extracts might influence the early loss. An attempt was made to start administration of the extract shortly after admission of the patient. Table VI gives a comparison of the per cent of total plasma lost (per 1% body surface burned) in the first 12 hours for the various groups. It does not indicate any clear advantage in this respect for either of the extracts employed.

TABLE VI

LOSS OF PLASMA IN PER CENT OF NORMAL DURING THE FIRST 12 HOURS DIVIDED BY THE AREA OF THE BURN IN PER CENT OF BODY SURFACE

Control		Eschatin		Whole Extract	
% plasma vol	per 1% area	% plasma vol	per 1% area	% plasma vol	per 1% area
2.8		2.3		2.4	

There is some evidence that adrenal cortical extracts may affect capillary permeability under certain experimental conditions. Vallee and Menkin⁴ Heuer and Andrus⁵ found that the combination of adrenal cortical extract and plasma seemed more effective in combatting shock due to the intravenous injection of the contents of an obstructed intestinal loop than plasma alone. Adrenal cortical extract was shown to decrease the loss of plasma volume that accompanies ether anesthesia by Ragan, and his associates.⁶

Adrenal cortical extracts have been employed in the treatment of burns at various stages by Wilson, Rowley, and Gray,⁷ Scudder,⁸ Einhauser,⁹ Ivory,¹⁰ and Elkinton,¹¹ with favorable clinical results. Most of these authors

used it after the period when burn shock is most severe. The present study is not concerned with its effect on toxemia nor can it be concluded from the present data that there may not be occasional cases in which it would be helpful in burn shock. However, the present cases do not indicate that it is of value for routine use in the management of burn shock. As better methods of following plasma volume in patients become available it is hoped that further studies may be made. Present conclusions apply only to the dosage level employed. The doses used were comparable to doses recommended in the treatment of Addisonian crisis.

CONCLUSIONS

Twelve patients with extensive superficial burns who received adrenal cortical extract did not retain plasma given by transfusion any better than did 13 control patients who received no extract. The local treatment consisted in tanning of all areas except hands and face and genitalia by one of the commonly used agents.

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USE OF ONE FLAP TO RESTORE EXTENSIVE LOSSES OF THE MIDDLE THIRD OF THE FACE*

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THE PURPOSE of this article is to present a simplified method for restoration of extensive losses of the middle third of the face, those involving the nose, upper lip and cheeks. Although the use of a forehead flap is a standard procedure for the repair of small losses, the use of a single flap in exactly this manner for such extensive losses of the face has not hitherto been reported, so far as I have been able to ascertain.

The method here advocated is not only the simplest and easiest one but also the quickest and most expedient. It would appear that a low forehead necessitating extension of the flap up into the hairy area of the scalp, might be a contraindication to use of the method. However, a variation of the



FIG 1—Preoperative photograph, right profile FIG 2—Preoperative photograph, left profile
FIG 3—Preoperative photograph, front view

procedure will be described so that part of the hairy scalp can be utilized in the male.

The patient, age 43, had sustained a gunshot wound to his face some months prior to his admission to the hospital. There were by that time no open wounds anywhere. Extensive loss of the middle third of the face was involved (Figs 1, 2 and 3). The entire nasal appendage had been destroyed, the upper lip was gone, the cheeks were obliterated from the level of the occlusal plane of the teeth upward to the malar bone. The entire maxilla was absent except for its most posterior portion, together with a small remnant of the hard palate containing only the second and third molar teeth on the left side. There was a remnant of the mucobuccal fold adjacent to these teeth on the left side. On the opposite side of the palate (the right)

*Submitted for publication with the permission of the Surgeon General of the U S Army and the Medical Director of the U S Veterans Administration

the remnant of the cheek was adherent to the existing portion of the maxilla in the region of the maxillary condyle. As can readily be observed from the photograph, the turbinates were exposed, markedly engorged and reddened. A fragment of the posterior portion of the nasal septum was present. From the angle of the mouth backward on each side there was a remnant of mucous membrane which was everted and attached to the scarred skin of the face.

Fortunately, the orbital floor on either side had not been obliterated and there was, therefore, no disturbance of vision. But other functions fared less well. The olfactory and gustatory senses appeared to be depressed.

FIG 4

FIG 5



FIG 4—The study model with the restoration built up in plastocene
FIG 5—Plaster impression of the plastocene restoration

The patient stated that food seemed tasteless and that he had difficulty in discriminating odors. Prior to insertion of a denture, speech was markedly affected, indeed, it was scarcely intelligible. There was marked improvement in speech after the denture was inserted and a still further improvement when the forehead flap was migrated into place.

The phenomenon of deglutition could be observed rather closely, and it was highly interesting to watch the movements of the soft palate and pharyngeal wall through the nasal chamber. The sphincter-like action of the velopharyngeal closure could be followed closely. The superior constrictor of the pharynx moved the posterior pharyngeal wall forward while the velum rose. The actions appeared to be not quite simultaneous, the constrictor movement starting very slightly in advance of the movement of the velum. When the velum had come into contact with the posterior pharyngeal wall thus

effecting a closure, the sphincter-like action continued for a brief interval to make the closure even tighter. Viewed from above, this tightening resembled a pout.

PLAN OF RESTORATION

The first step in planning the restoration was to make a plaster cast of the face for study. Upon this study model, the proposed restoration was built up in modelling clay (Fig 4). An impression was then taken of the proposed restoration to provide a negative (Fig 5). A thin coating of latex rubber was poured into the negative mold and permitted to dry. When

FIG 6—The latex pattern



FIG 6

FIG 7—The latex pattern, laid out on the flat

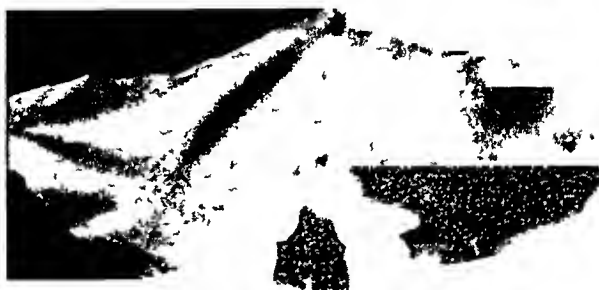


FIG 7

FIG 8—Alternative method of flattening the pattern which avoids a long, narrow flap in the columellar region and midportion of the lip

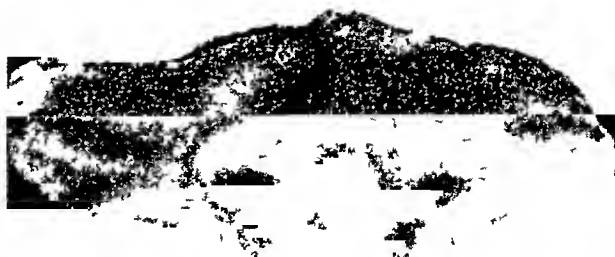


FIG 8

it had dried completely, the latex was peeled from it. In this way the actual contour of the final restoration was obtained through a latex rubber pattern which could be flattened out (Fig 6).

An extra latex pattern heavier than the first, was fashioned and colored to match the patient's skin. This was worn by the patient as a mask, held in place by an elastic band placed around the head. It provided a far more satisfactory and comfortable dressing for the patient than had the gauze previously worn, and attracted less attention. The patient, who had showed

signs of depression over his unhappy condition, became more cheerful and comfortable when the latex pattern was provided as a mask. He then went freely about the hospital and made no attempts to shun people.

The next step in planning was to take actual measurements of the first latex pattern, and this could be done only by reducing the pattern itself from a three-dimensional to a flat two-dimensional surface. Accordingly, the pattern was cut from the free margin of the lip to the floor of the nostril on either side of the philtrum (Fig 7). (Figure 8 shows an alternate method of flattening the pattern.) Precise measurements of the flap were then taken and the flap itself reproduced in an exact tinfoil duplicate which could be boiled and utilized at the operative field. By placing the flattened pattern on the patient's forehead, it could instantly be determined

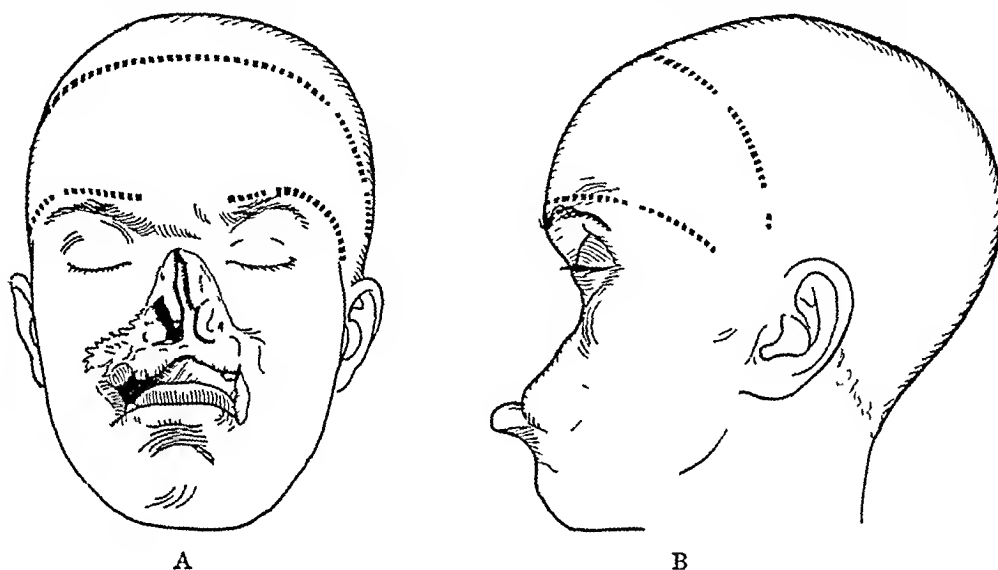


FIG 9—The broken lines indicate the incision for the forehead flap. Note the bridge of unincised skin in the glabella region. While not absolutely essential, the bridge will prevent possible disaster through circulatory insufficiency.

whether or not the forehead was high enough to be utilized without encroaching upon the hairline. In this case the forehead was adequate.

The plan selected in this particular case involved utilization of a double pedicle flap from the forehead, encompassing practically the entire forehead between the level of the eyebrows and the hairline, with a pedicle on either side in the region of the temple. This flap was to be lined with skin and later migrated, maintaining both pedicles and being swung downward to the proper level just as the visor of a medieval armored helmet would be brought down. The nose could then be shaped-up by exactly reversing the procedure which had been used to flatten the latex pattern, in other words could be built up from two to three dimensions and supported by a denture and nose piece.

EXECUTION OF RESTORATION

All the operative procedures were carried out under local anesthesia, the anesthetic of choice being two per cent procaine with a few drops of 1 to 1,000 adrenalin chloride per ounce of procaine.

At the first operation, the forehead flap was formed and lined. Figures 9 A and B show the outline of the incision. The tinfoil pattern was placed upon the forehead in the proper position and the incisions made as shown in the sketch. It will be noted that a bridge of unincised skin was left in the



FIG 10 —The forehead flap has been undermined throughout its extent and a free skin graft, taken from the abdomen, lines the flap, and covers the donor area

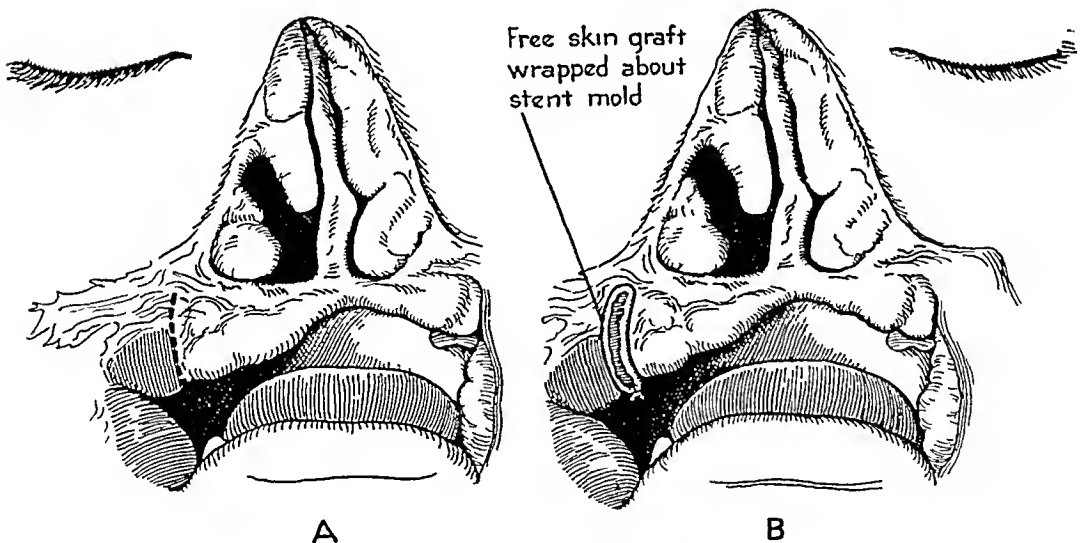


FIG 11 —Buccal inlay to provide retention for the denture

A The broken line indicates the incision in the region of the maxillary condyle on the right side. The incision had to be carried up beyond the bulge.

B The free skin graft wrapped, raw surface cutward, around the stent mold and inserted in the pocket to form a new gingivobuccal gutter.

glabella region to transmit the angular arteries and veins in order to insure against circulatory failure. This bridging may not be absolutely essential but it does afford security and certainly avoids possible disaster through insufficient circulation. The entire area between the incisions was undermined

and the flap raised up. The pedicles in the temporal region on each side were tubed.

The flap was lined at this operation and the donor area skin-grafted at the same time. Two intermediate thickness skin grafts about the size of the pattern were taken from the abdomen. One skin graft was placed over the donor area, trimmed to shape, and the edges of the graft sutured to the margins of the donor area. The other skin graft was inserted beneath the flap so that its cut surface was in contact with the under surface of the flap, thus providing a lining. The edges of this second graft, after they were trimmed, were sutured to the margins of the flap.



FIG 12—The denture *in situ*. The forehead flap is ready to be migrated. The lining of the flap and the covering of the forehead have entirely healed and the bridge of skin in the glabella region has been severed.

Molded moistened sterile absorbent cotton covered with vaselined gauze (Fig 10) was inserted between the lining of the flap and the free skin graft covering the donor area. The flap itself was carefully covered with a pressure dressing. After ten days, the dressing was removed, the grafts—both flap lining and donor area covering—had taken *in toto*. All the sutures were removed and a pressure dressing reapplied.

Several weeks were permitted to elapse so that the flap might consolidate firmly. During this interval, the problem of the prosthesis was attacked and solved. One perplexing point in regard to the prosthesis was the matter of retention. Complicated methods had to be rejected since it was felt that a prosthesis should be so simple in design that it could be inserted and removed for cleansing by the patient at will. Furthermore, it should be of such construction that it could be repaired by any competent

dentist. Much thought and study were given to these requisites. It was finally decided that some method of retention should be provided on the patient's right side. Retention on the left side could consist of simple dental clasps about the two remaining teeth on that side of the maxilla. However, adherence between the remnant of the maxilla, its condyle, and the scarred remainder of the cheek, presented a stumbling block. This obstacle was overcome by resorting to a buccal inlay in that region so that the basic denture might encompass the condyle of the maxilla for retention on the right side.

Prior to the second operation itself, the basic denture was constructed of acrylic resin. It consisted of a palatal portion with clasps on the left side for the two surviving molars and a small rim anteriorly to fit over the

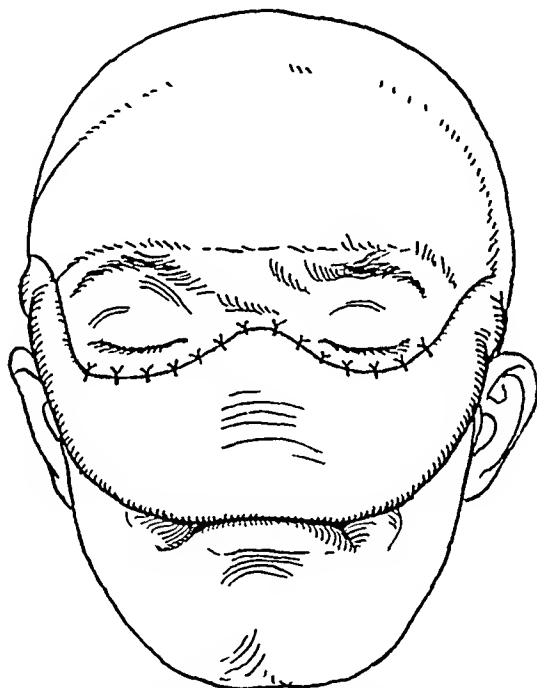


FIG. 13.—The flap has been migrated and sutured to the upper margin of the defect.

free edge of the palate and extend very slightly on to the floor of the nose. The right side of the denture was cut away and an addition to it was to be molded at the time of operation.

It was important to construct the denture and to fit it properly prior to migration of the flap not only because it would actually be difficult to take an impression and fit a denture once the flap was migrated, but also because it was desirable to have the denture in place so that the flap might rest against it and to some extent be immobilized.

At the second operation, the buccal inlay was performed. But first the bridge of skin in the glabella region was severed, the lining of the flap sutured to the covering, and the incision in the donor area closed. An incision was then made between the cheek and the condyle of the maxilla, extending upward well beyond the bulge and also posteriorly beyond the rounded eminence (Fig. 11 A). Stent was molded into this cavity and

an epidermic skin graft, taken from the thigh, was wrapped, raw surface outward, about the mold, which was inserted into the cavity and sutured into place (Fig 11 B) However, before the skin graft was sutured into place, the denture was inserted and stent molded in the cavity and attached to the denture Denture and attached stent were removed in one piece This provided a means of obtaining an extension of the denture into the newly created pocket (Stent and denture were reproduced in one piece so as to be available after skin graft had taken) About five days after the insertion of the skin graft, the mold was removed, the graft found to



FIG 14—The migrated flap, sutured along its upper margin, is supported by the denture, which prevents it from falling backward

be viable, and the denture with its extension up into the newly created buccal fold was at once inserted

This early use of the denture prevented contraction of the graft and maintained the new sulcus The denture required minor adjustment from time to time However, the patient persisted in using it and, finally, an excellent sulcus was obtained with good retention for the basic denture (Fig 12)

At the third operation, the pedicles on either side were lengthened The upper border of the flap was freshened, and the two layers (lining and covering) separated for a few millimeters An incision was made beginning on one side in the malar region and extending across the upper margin of the defect to the malar region of the opposite side This incision provided two edges, the outer of which was sutured to the skin covering of the flap, and the inner sutured to the lining of the pedicle (Figs 13 and 14)

The flap healed rapidly in its new position and, after an interval of about three weeks, one pedicle was severed and the flap sutured to the cheek in layers (fourth operation). Then, after a similar period, the pedicle on the opposite side was severed and treated in the same manner (fifth operation). In each instance the remnant of the pedicle which had been tubed was opened up and returned to the forehead.

At this stage the nose piece of the prosthesis was attached to the denture. Various types of joints and unions were considered, but here, again, complicated arrangements were discarded in favor of a simple direct fusion.

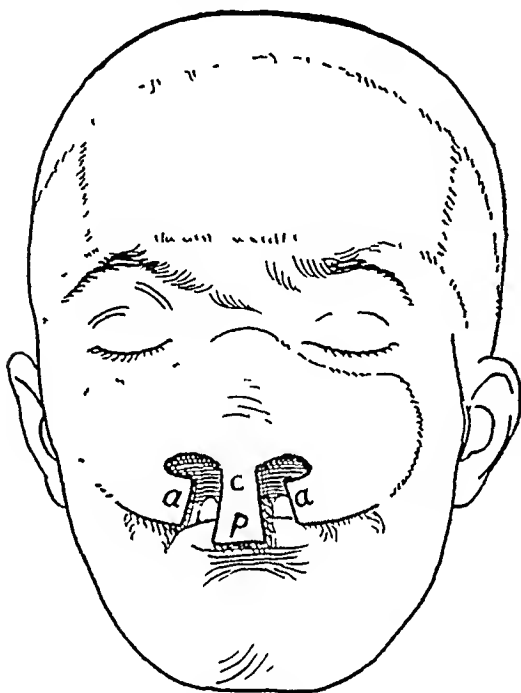


FIG 15

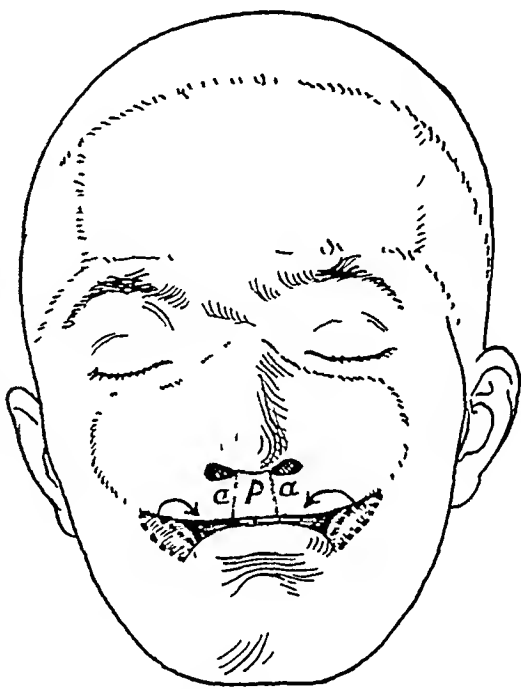


FIG 16

FIG 15—Trimming the flap to form the nose. This is similar to figure 7. The central portion of the flap *c* and *p* will form the columella of the nose and the philtrum region of the upper lip respectively. The portions of the flap *a* on each side will be brought medianward to meet *p*. This step is the direct reverse of flattening the pattern. Reference to figure 8 as an alternative method is suggested, for this will avoid the long, narrow flap *cp*.

FIG 16—The nose has been formed, the lip flaps *a* have been united to the philtrum *b* to form the upper lip. The vermillion border flap on each side indicated by the broken line contiguous to the angle of the mouth on each side, will be raised up and migrated to the lower margin of the restored upper lip, which is freshened to receive the flaps.

of the nose piece with the denture itself. The nose piece, like the denture, was constructed of acrylic resin.

At the sixth operation the flap was trimmed to form the nose. Reference to Figures 7 and 15 will clarify this step. Vertical incisions were made in each side about three-eighths of an inch from the midline of the flap beginning at the lower free margin. These incisions extended vertically upward for a distance equal to the normal height of the lip. Here began elliptical incisions to form the alar rim, curving first inward and upward, then outward and downward. At a point which would be somewhat medial to the lateral limit of the alar attachment, the incision turned sharply and descended vertically to the free margin of the lip. The portion of the lip thus excised approximated roughly in shape the head of a golf club and a

portion of its thickened shaft. The central part of the pedicle now corresponded to the philtrum and the point where the curve began represented the beginning of the columella. The oval or elliptical portion of the excision corresponded to the alar rim. Along this site, the covering was sutured to the lining, thus forming the nose, and the continuity of the lip brought about as shown in Figures 15 and 16.

About one month later, the final operation was carried out. At this stage the vermilion border was restored to the reconstructed lip. This border was taken, in the form of hinge flaps, from the mucous membrane which extended along the edge of the defect immediately contiguous to the angle of the mouth. The pedicle of the flap remained at the angle

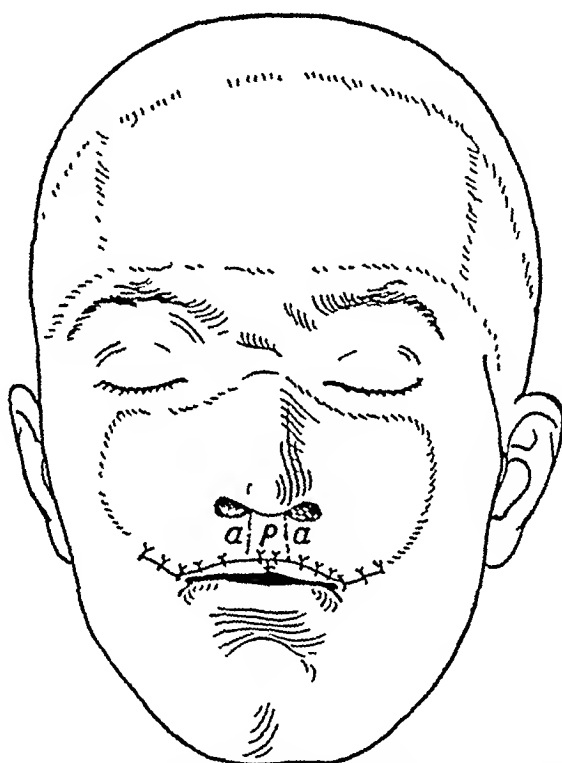


FIG. 17 —The migration of the vermilion border flaps completed and the oral fissure reduced to normal size.

of the mouth, while the incision extended laterally from this point along the junction of the skin and mucous membrane backward for a distance equivalent to half the width of the upper lip (Fig. 16). The lower border of the reconstructed upper lip was pared, the vermilion flaps migrated so that their distal extremities met in the midline, and the vermilion border flap sutured into place in the reconstructed lip (Fig. 17). Figures 18, 19 and 20 show the reconstruction—final stage. Figures 21, 22 and 23 show various views of the denture.

The method here described can, with but little modification, be utilized either for more extensive losses—that is, those of greater height than the loss herein encountered—or else for those cases where the forehead itself is exceedingly low. In the latter case, the necessity for encroaching on the hair-bearing scalp is at once apparent. If such a hair-bearing flap were

FIG 18



FIG 19



FIG 20



FIG 18—The completed restoration, right profile

FIG 19—The completed restoration, left profile

FIG 20—The completed restoration, front view This photograph was taken shortly after operation. In time the flap will drape itself about the supporting nose piece so that the nasofacial angle will become sharper. The upper lip has a somewhat backward tilt. This can be corrected by a revision or an Abbe type of operation.

FIG 21



FIG 22



FIG 23



FIG 21—The prosthesis, front view. The entire prosthesis is made of acrylic resin in one piece, the nasal portion being perforated so that it is possible to breathe through the nose.

FIG 22—The prosthesis, side view. One great stumbling block in restorations of this type is the fact that if the oral opening is made large enough to permit insertion and removal of the prosthesis at will, appearance is sacrificed, while if the opening is smaller, appearance is better but difficulty is encountered in inserting and removing the denture.

FIG 23—Posterior view of the denture. Note the rim which extends upward to rest on the anterior margin of the palate defect.

migrated in the manner described herewith, the hair-bearing skin would be close to the lower eyelids and the root of the nose. This may be avoided by transposing the flap (Fig 24). The double pedicle flap is made and lined in the usual manner. However, instead of being migrated in visor-like fashion, one end of the pedicle can be severed and transposed so that it is migrated to the cheek on the same side as that of the undisturbed pedicle. When the migrated end has healed, the remaining forehead pedicle may then be severed and transposed to the opposite cheek. In this way, the hair-bearing skin will be brought down toward the upper lip and cheeks, thus simulating the hairy area of the upper lip in the male subject. In the female patient, epilation by irradiation or by needle is theoretically possible but is not recommended. If it were absolutely necessary to extend the flap up into the hairline, the hair follicles could be destroyed surgically.

by shaving them off on the under surface of the skin at the time the flap was undermined

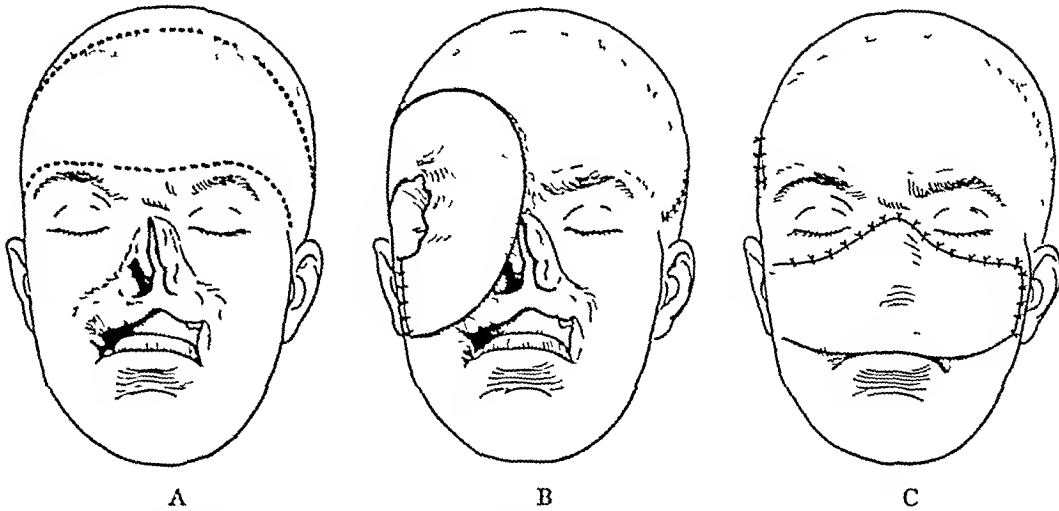


FIG 24—A method of reversing the flap so that, in the male subject, if unavoidable, the hairy portion of the forehead may be utilized and will form the mustache
A The outlines of the flap extending into the hairy scalp
B The left side of the flap migrated to the right side of the defect
C The migration completed. The hairy portion of the scalp has been brought down to the region of the upper lip where it will form a mustache
The alternative method of forming the nose, as shown in Figure 8, should be used to avoid hair bearing skin in the columella

SUMMARY AND CONCLUSIONS

In general, one-case reports are likely to be inconclusive in nature, but it is quite evident that the method presented here is entirely workable. While it is readily conceded that the result shown may leave much to be desired, it cannot be denied that the method offers the simplest and easiest solution to the problem of repairing an extensive and hideous type of disfigurement. Since it is to be expected that similar wounds will be encountered in the future, the report is presented at this time in the hope that it will be useful and may serve as a basis for a more or less standardized method of repair for this type of disfigurement. Further experience will no doubt lead to improvements both in technic and in result. For instance, the flatness or backward tilt of the upper lip may be corrected by a transplantation from the lower lip (the Abbé operation).

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PARTIAL FUNDUSECTOMY (PROXIMAL GASTRECTOMY)*

REVIEW OF 24 CASES

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OSHKOSH, WIS

THIS COMMUNICATION is primarily a "follow-up" on the case of recurrent intractable duodenal ulcer treated by partial fundusectomy (proximal gastrectomy) on December 14, 1931, and reported in ANNALS OF SURGERY, for August, 1932¹ A synopsis of the above report follows

Case Report—H P, married, male, millworker, age 24 Referred by Dr T D Smith, of Neenah

Chief Complaint First seen in September, 1931, with typical symptoms of duodenal ulcer, increasing in severity, with recent vomiting, weight loss and night pain Onset about six months previously, following a 15-months symptom-free interval after a second stomach operation

Previous History "Rheumatism ever since a baby" At about ten years of age, for one year was invalided because of "heart disease" When 19 years of age "acute rheumatic fever" followed by tonsillectomy Gastric symptoms developed suddenly at age 21 After about six-months of typical duodenal ulcer history acute perforation occurred on May 4, 1928 Celiotomy, with closure of acute perforation of duodenal ulcer and a gastro-enterostomy (Dr C J C) was performed This was followed by a symptom-free period until return of gastric symptoms in June, 1929 Medical and dietary management was not successful and, in August, 1929, an acute massive hematemesis occurred At this time "acute endocarditis" was diagnosed In September, 1929, roentgenologic examination revealed a deformed duodenal cap, with the stoma patent and functioning One month later a second, and in December, 1929, a third acute massive hematemesis occurred

In January, 1930, a second celiotomy was performed in which a jejunal ulcer was excised and a gastro-enterostomy taken down (Dr C J C) This operation was followed by a symptom-free interval to March, 1931

Family History Father dead because of "stomach ulcer" Mother living after operation for gallstones Brothers—four Two dead one due to "flu," the other from "stomach ulcer" Two living, one after gastro-enterostomy for "stomach ulcer" One with "stomach ulcer" Sisters Two living after gastro-enterostomy for "stomach ulcer"

Physical Examination Practically negative except for evident weight loss, tenderness in epigastrium and right hypochondrium and hypotension Laboratory findings Secondary anemia Test meal High acidity, with no retention Roentgenologic examination Duodenal cap deformed, but no retention *Diagnosis* Recurrent duodenal ulcer

In December, 1931, a third celiotomy, during which a partial gastric fundusectomy (Fig 1) was performed (Dr F G C)

The "follow-up" since the operation in 1931, and the report in 1932, may be summarized as follows

The patient has met with many psychic and physical traumata, some of which have been at times suggested as exciting factors in the development of peptic ulcer, such as loss of job, financial reverses, improper and inadequate food with "overwork and worry," various illnesses, accidental injury to hand, with infection, deformity and crippling loss of function, leading a year later to amputation of a finger, serious abdominal and cranial trauma with shock, and minor accidents and infections All without evidence to date (after 12 years) of recurrence of peptic ulcer

* Submitted for publication June 1, 1943



FIG 1—Resection of fundus of stomach in treatment of peptic ulcer

In January, 1932, a nontoxic adenoma of the thyroid was discovered. He presented no gastric symptoms, and the first postoperative test meal showed free hydrochloric acid 0, total acid 37, with no retention.

In June, 1932, the patient experienced a recurrence of his "endocarditis," but with no gastro-intestinal complaint.

In July, 1932, a barium meal revealed a deformed duodenum, with stomach returned to seemingly normal size and position. Scar of fundusectomy is seen as a defect

in the greater curvature The second postoperative test meal revealed free hydrochloric acid 0, total acid 40, with no retention

In November, 1934, for about a week, he had an attack of "flu," with "heart palpitation," temperature and constipation A third postoperative test meal showed a normal curve for free hydrochloric acid 37, total acid 58, with no retention Barium meal Same as at previous examination

In December, 1934, an accident to his hand resulted in a severely infected left index finger, with lymphangitis In November, 1935, this finger was amputated because of deformity and loss of function A fourth postoperative test meal showed free hydrochloric acid 19, total acid 36.5, with no retention

On June 15, 1937, a bursting emery wheel caused severe injury to his abdomen, face and skull—shock, abdominal pain, tenderness, muscle spasm, rigidity, with lacerations, contusions and abrasions of abdomen, face and scalp Recovery was prompt, and he was discharged from the hospital on June 22, 1937, with no abdominal symptoms

In September, 1940, report by Dr T D Smith "Working daily in foundry Gain in weight, no stomach symptoms"

In August, 1941, he had an attack of so-called "stomach flu," followed by recovery in a week Other members of the family complained of same symptoms

In September, 1941, after vacation hunting fishing and over exertion, he experienced "distress" in epigastrium, not a pain, only "soreness," with no digestive disturbance Relief followed a few days of rest and counter irritation A fifth postoperative test meal showed free hydrochloric acid 20, total acid 60, with no retention Roentgenology showed same as at previous examinations

In November, 1942, Doctor Smith reports "Auto accident on hunting trip in north woods Complaint of abdominal pain of a few days duration" In February, 1943, "Hospitalization with infected hand, temperature, chill, cellulitis No abdominal or gastro-intestinal symptoms" In July, 1943, "Continued absence of gastro-intestinal symptoms The patient is at work daily and considers himself well"

The postoperative elapse of time and unfavorable conditions and circumstances since the operation in 1931, in this case, would serve as a real test for the method of treatment But before any evaluation of results may be attempted, many more cases must, of course, be studied

Since December, 1931, I have records of 24 cases in which partial fundus-sectomy (proximal gastrectomy) has been carried out In 1938 the results in 14 cases (the longest postoperative interval at that time was six years) were reported²

In 1935 additional cases were included in a discussion³ of "The Problem of Intractable Peptic Ulcer"

In the 24 cases there were two deaths, one on the 14th postoperative day due to uremia, the other, after return of symptoms and reoperation one year later, at which time additional fundus was removed Death followed on the 8th postoperative day, due to ileus under an adhesion at the site of a previous appendectomy In two cases the remote result is unknown Of the remaining 20 cases, 19 have been symptom-free

The unsatisfactory result (an intractable case with a history of three previous celiotomies) was operated upon September 24, 1938³ In this case the symptoms, returned in about six months, and an acute massive heme-temesis necessitated another operation November 20, 1939, at which time

an old duodenal ulcer (probably present at the time of the previous operation for jejunal ulcer) was removed and a pyloroplasty performed. Convalescence was uneventful and since then the patient has remained entirely symptom-free and is at work daily.

Clinically satisfactory results in 19 cases have occurred, despite return to normal hydrochloric acid secretion and return to normal stomach size, tonicity and motility in five cases that have been checked by test and barium meals. Such return to normal gastric function was found to occur experimentally by the writer,¹ Watson,² Seely and Zollinger,⁶ Fauley and Ivy,⁷ and Zollinger.⁸ The postoperative interval was over ten years in four cases, between ten and five years in seven cases, four years in one case, three years in two cases, two years in three cases, less than one year in two cases.

In an attempt to evaluate these results, it is well to remember that each case was very complicated, and definitely intractable. The appendix had been previously removed in 18, gastro-enterostomy had been performed in nine cases, cholecystostomy in one, taking down of a gastro-enterostomy in three cases, acute perforation had been closed once in eight cases, and twice in three cases, acute massive hematemesis had occurred in three cases, combined jejunal and duodenal ulcers in one case, "kissing" duodenal ulcers in one case and gastrojejunal fistula in two cases. Under these unfavorable circumstances the results are definitely encouraging.

This series of 24 cases is, of course, too small and the postoperative elapse of time since December, 1931, is too short (recurrences after ten or more years are not uncommon) to make the results of practicable statistical value.

This report is being made with the aim of encouraging others to give this method a trial in the management of suitable (*i.e.*, intractable nonobstructive) cases of duodenal ulcer.

If these results can be confirmed by others in larger numbers, it would seem to call for favorable consideration, before performing the presently accepted distal gastrectomy, which is based upon the unproven Edkin's theory,⁹ and results in serious interference with normal gastro-intestinal function. This more formidable procedure may, if necessary, be carried out at a later time.

These cases were instructed to continuously and permanently avoid tobacco, alcohol and salt, and to take frequent feedings in small amounts, of no special diet.

Such a regimen is advisable after any type of surgical treatment for duodenal ulcer, as the operation is but an incident, often a most important incident, between pre- and postoperative management.

SUMMARY

A review of the postoperative history in a case of partial fundusectomy (proximal gastrectomy), operated upon in December, 1931, and reported in *ANNALS OF SURGERY*, of August, 1932, in which the result has been very satisfactory despite many unfavorable postoperative circumstances and conditions.

A review of 24 cases of intractable nonobstructive duodenal ulcer in which this type of operation has been carried out, two of which died and two were lost sight of

The clinical results in 19 of the remaining 20 were favorable, the other has remained symptom-free for three and one-half years after reoperation

The postoperative period is over ten years in only four

This report is made with the aim of encouraging others to give this method a clinical trial in suitable nonobstructed cases of intractable duodenal ulcer

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THE PEPTIC ULCER AND CHRONIC GASTRITIS[†]

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IT HAS LONG BEEN FELT by all who are interested in the pathology of the stomach that the common lesions of peptic ulcer and carcinoma are associated with changes throughout the gastric mucosa. The common term of chronic gastritis has been applied by the clinician, the pathologist, the radiologist, and the gastroscope to a wide variety of findings, and each has developed a scheme of classification reflecting the position from which the evidence has been surveyed. The elements of inflammation, with congestion, edema, and cellular infiltration have been seized upon by all as of primary importance and have been woven into every definition and classification. According to their varied interests observers have attempted to establish chronic gastritis as a diagnostic entity which may be present independent of other pathology. Some have theorized, or attempted to establish a relationship, between such an entity and the peptic ulcer or gastric carcinoma. That their efforts have fallen somewhat short of this goal is shown by the lack of correlation of findings and the lack of any clear-cut definition of chronic gastritis. This term is too well established in our vocabulary to be discarded, so it must be used, but an attempt is made to define its meaning clearly.

This communication is a preliminary presentation of a project undertaken under Dr. Shields Warren, at the New England Deaconess Hospital, Boston, Mass., and continued under Dr. Arthur P. Stout, in the Department of Surgical Pathology at the Presbyterian Hospital, New York. Over a two-year period, a total of 213 surgically resected stomachs were examined. These specimens were resected for duodenal ulcer, gastric ulcer, gastric carcinoma, lymphosarcoma, or in the course of resection of the head of the pancreas. The material was obtained directly from the operating room and, avoiding all possible trauma due to handling or washing, fixed in Zenker's fluid with five per cent glacial acetic acid or Bouin's fixative. The number of blocks taken varied with the extent of the resection. There were seventeen charted sites in the complete specimen including terminal esophagus and duodenal bulb.

Early in the present investigation it seemed apparent that if a relationship between chronic gastritis and peptic ulcer or gastric carcinoma was to be established, its basis was to be sought in changes in the epithelial elements of the mucosa, rather than in the inflammatory elements. Believing that these inflammatory manifestations, which have been adequately described by numer-

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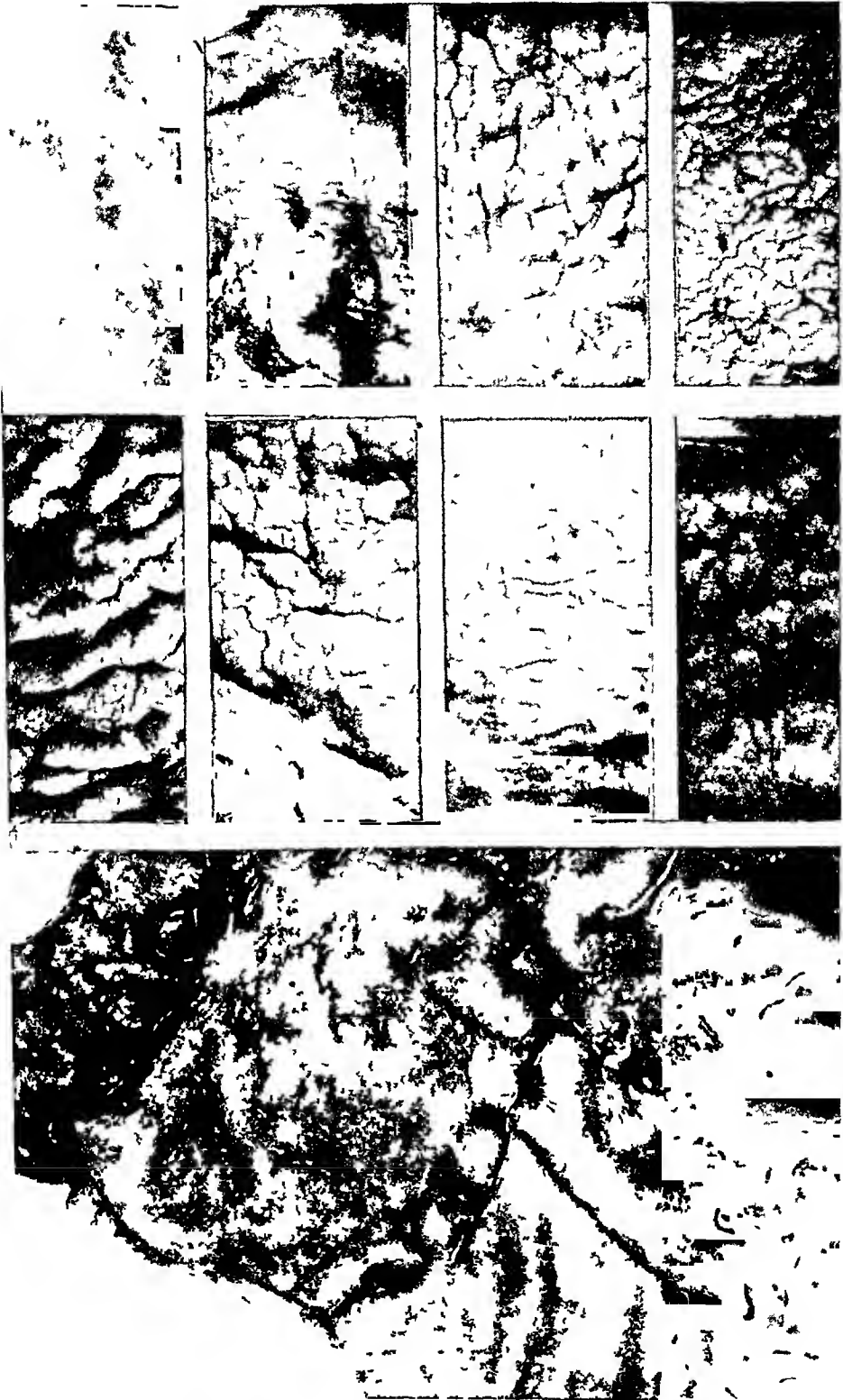


FIG 1—The appearance of minimal gross lesions
FIG 2—Stellate superficial ulcers, with communicating fissures on posterior wall of antral region. Pylorus and duodenum to the left

ous investigators, are not of a specific type, and only roughly parallel the disease process, they will not be elaborated in any detail

In the callous peptic ulcer the continuity of all layers of the gastric wall, the mucosa, submucosa, and muscularis, is abruptly interrupted. The base of the ulcer is in dense fibrous tissue, frequently external to the muscle coat. This lesion may heal but a permanent scar marks the site. Dense fibrous tissue fills the defect, and epithelium grows in from the margin, first, in a single flattened layer, then forming gastric pits and occasionally glands with chief and parietal cells. The elements are apt to be distorted with branching and dilated cystic forms. The muscularis and muscularis mucosae never completely regenerate.

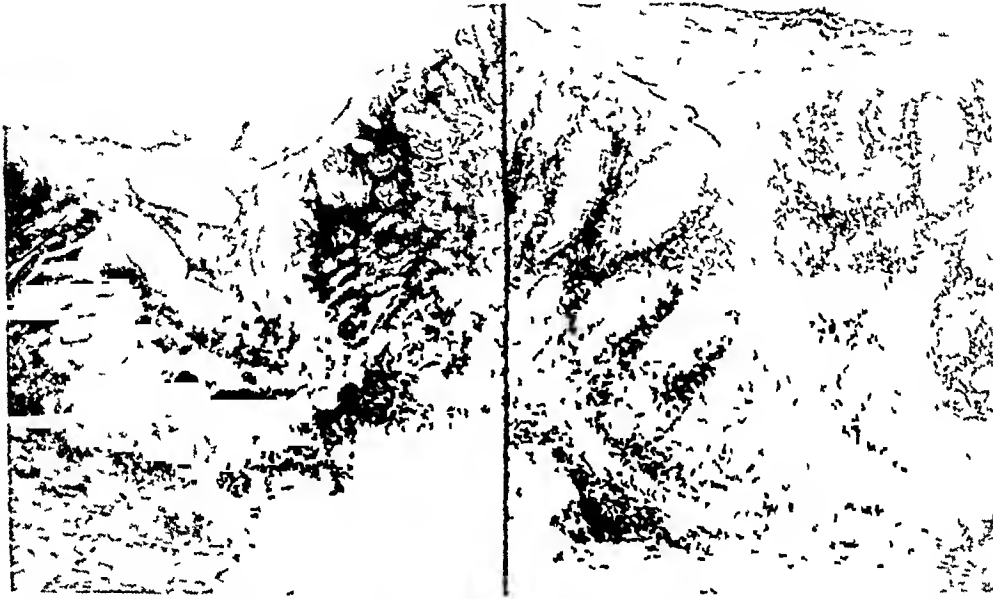


FIG. 3—Superficial ulcer limited by muscularis mucosae

FIG. 4—Almost healed mucosal ulcer, with mucous plug

As gastrectomy has come to be more readily undertaken, the pathologist has encountered less typical lesions, but ones which differ from the callous peptic ulcer only in degree. They may penetrate only partly through the muscle coat, or only into the submucosa. They are attended by a commensurate degree of fibrosis and granulomatous reaction, and heal with minor scarring of the muscle coat and submucosa and some distortion of the mucosal elements.

The ulceration may be limited by the muscularis mucosae. This lesion, particularly, has come under observation as a result of surgery undertaken early in the history of the ulcer patient or before prolonged medical supervision has produced a remission of symptoms. Phlegmonous ulceration has been included in classifications of gastric lesions but this has frequently been applied to the extensive superficial erosions encountered at postmortem whether due to autolysis or a manifestation of a generalized overwhelming disease. The lesions here referred to are not always grossly evident until similar ones have first been identified microscopically. They are minute stellate, focal, or irregularly linear ulcerations (Fig. 1). Occasionally two or more small stellate lesions may be continuous through connecting fissures,

active or healed (Fig 2) In microscopic preparations these are limited by the muscularis mucosae and covered by a thin zone of fibrinopurulent exudate and granulation tissue The underlying submucosa shows some edema and a slight increase in fibrous tissue The adjacent mucosa flows into the defect so that the gastric pits and glands are directed into the defect and lie at right angles to their former position (Figs 3 and 4) A mucus plug is commonly seen to fill the defect

These lesions are always multiple and when they heal the imprints persist These have been found in every surgically resected stomach examined If the gastric mucosa be examined closely it will be observed that it has a pebbled or cobblestone character that is most marked in the pyloric region and along the lesser curvature In the stomach of the chronic ulcer patient



FIG 5—Healed mucosal lesion or crypt
Note orientation of gastric pits



FIG 6—Healed mucosal lesion or crypt
of lesser magnitude than Figure 5

this effect is marked It is least evident when the pathology is minor, of short duration, or in young individuals This pattern is due to a network of shallow fissures outlining mounds of gastric mucosa When the pebbling is coarse the mounds of mucosa so marked out may have a central depression or fovea, so that they present an umbilicated appearance (Fig. 1) In sections active, healing, or healed stages may be encountered in serial blocks of a single fissure In healing, the defect is not filled in by fibrous tissue but regenerating epithelium creeps across the base from the surface mucosa which dipped into the ulcer and formed its side walls A crypt-like formation results, into which adjacent gastric pits are directed, and this configuration is not lost even when the regenerated epithelium recovers normal mucous secreting properties and some regeneration of pits and glands has occurred (Figs 5 and 6) The term "crypt" will be applied to this configuration in which the surface epithelium dips to the region of the muscularis mucosae, and adjacent gastric pits and glands, losing their usual orientation, are deflected into the depression at right angles to the surface

A series of finely graded lesions can thus be traced in retrograde fashion from the callous peptic ulcer to the minute mucosal ulceration. At no point in the series can a line be drawn to demarcate one lesion sharply from another. When a peptic ulcer is present it should, therefore, be considered only the most obvious example of multiple lesions involving the gastric mucosa. It would follow that the absence of a callous peptic ulcer in the presence of multiple lesser lesions does not materially alter the fact that such a specimen may still be an "ulcer stomach."

But these are not the minimal lesions to be identified on careful microscopic inspection of gastric mucosa. A further series of lesions, finely graduated as to severity and size, can be identified within the mucosa. In order of decreasing severity, the first of these, considered to be the connecting link between the ulcerated and intramucosal lesion, is a focus of necrosis which occupies the full-thickness of the mucosa. There is an intense poly-



FIG 7—Focal necrosis in gastric mucosa, with polymorphonuclear leukocytic infiltration

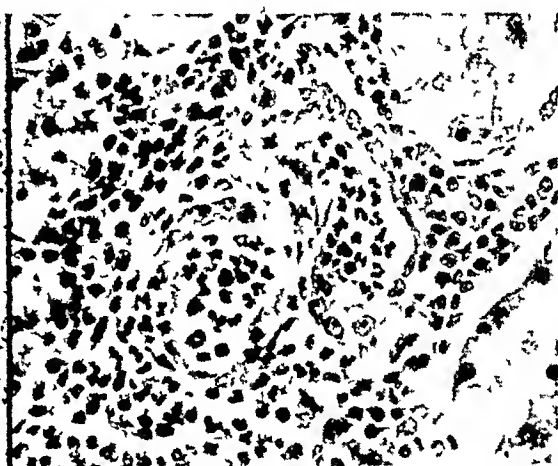


FIG 8—Necrosis of isolated gastric glands, with polymorphonuclear leukocytic infiltration

morphonuclear infiltration, with edema about a gastric pit and gland, or several of such units, which are undergoing degeneration and necrosis (Fig 7). It is suggested that the reaction may proceed to a break in the mucosa with the formation of the mucosal ulcer described, with either eventual healing resulting in the typical crypt, or if this does not occur, to a fully developed callous peptic ulcer. Smaller foci of necrosis are more frequently encountered involving only a single gland (Fig 8). Polymorphonuclear leukocytes are clustered about the gland, within the epithelium, and within its lumen. The epithelial cells and their nuclei are pyknotic and in the disintegration of the gland may form an apparent syncytial mass. There may be an accompanying infiltration of lymphocytes and histiocytes of varying intensity.

Isolated glands which undergo degeneration without exciting a prominent inflammatory response may also be encountered. The pale outline of the basement membrane can be identified and the faint outlines of disintegrated chief and parietal cells from which nuclei have completely disappeared. An indistinct cluster of pale eosinophilic granules may identify the remnants of a parietal cell (Fig 9). Other glands at a slightly earlier stage may demonstrate a vacuolar degeneration of chief and parietal cells with a loss of granule definition and a swelling, pyknosis, or disappearance of the nucleus (Fig 10). That this is not an artefact or autolysis is evidenced by the preservation of all cellular details of adjacent uninvolved glands. Parietal cells are well known for their ability to persist even in autopsy material, but even the chief cells, which undergo disintegration much more readily, can, in these adjacent glands, maintain cellular outline, cytoplasmic basophilic granules, and nuclear detail. In another alteration in gastric glands that is encountered with some frequency, the lining cells,

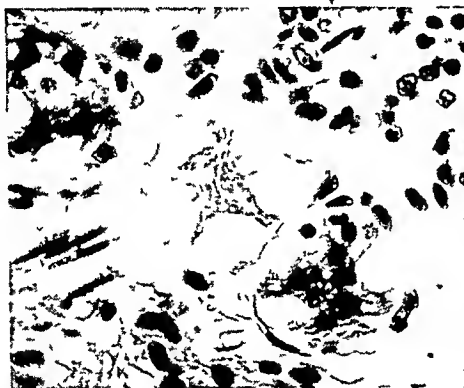


FIG 9—Complete degeneration of isolated gastric gland

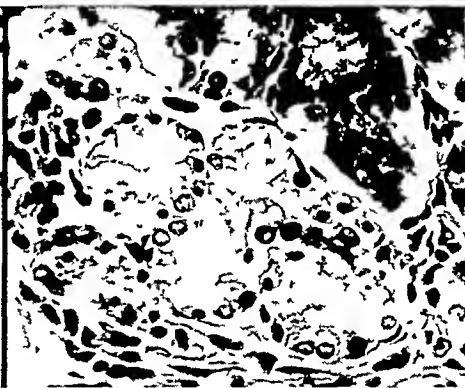


FIG 10—Localized degeneration of gastric glands

although well preserved are somewhat smaller than usual, crowded together, and have a pale cytoplasm so that they may bear a close resemblance either to the cells of the pyloric glands or to Brunner's glands of the duodenum. In some examples a parietal cell or a chief cell may be interspersed among these relatively undifferentiated cells (Fig 11).

It is more difficult to trace the process of repair which must follow upon these intramucosal foci of necrosis and degeneration. It would seem that the more severe manifestations should leave some scar in resolution. This may be a focus of increased density of connective tissue resulting in some shrinkage and a depression of the surface mucosa to form an irregularity which falls short of the well defined crypt. The lesser lesions will leave proportionately less apparent scars. The vacuolar degeneration and disintegration of cells of a gland without an accompanying polymorphonuclear reaction may be the manner whereby the process of wear and tear disposes of exhausted gastric glands. Replacement may occur by regeneration from the neck region so that reformed glands are first lined by undifferentiated cells (Fig 11). These degenerative changes are paralleled by a regenerative

response on the part of the germinal cells in the neck region. The degree of mitotic activity which may be quite marked in this region is roughly proportional to the severity of the degeneration and necrosis (Fig. 12).

A series of changes has thus been outlined which proceeds by imperceptible stages from a phenomenon of degeneration and repair, which may well be a normal process, to the picture of the typical peptic ulcer. This uninterrupted series of lesions, which is primarily concerned only with the epithelial elements of the gastric gland, is proposed as the basis of chronic gastritis. From this process the peptic ulcer cannot be separated. Chronic gastritis, so defined, cannot be thought of as a condition which may precede or be associated with the peptic ulcer but includes it. This conception of chronic gastritis makes it possible to interpret as part of a single process a number of findings which have previously seemed unrelated or contradictory. Since the peptic ulcer is not the sole or even in the disease process the most important lesion in the stomach of the ulcer patient, it makes understandable the common clinical experience of a positive symptomatology and a response to therapy in the absence of a proved diagnosis.

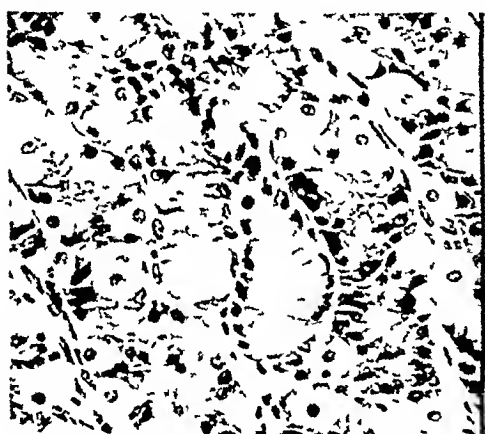


FIG. 11—Gastric glands lined by cells which have not differentiated to chief and parietal cells

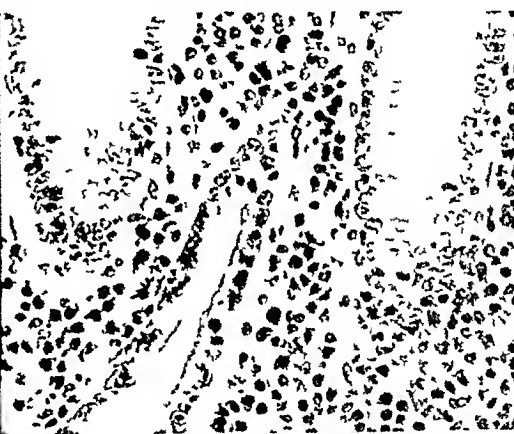


FIG. 12—Mitotic activity in germinal epithelium of the neck region between gastric pits and glands

Surgical material has not been adequate for an extensive study of duodenal mucosa. The portion of duodenal bulb resected is usually very short, and even this is apt to be in part destroyed by clamping, transection, and cautery. Not only is it difficult to throw new light on its pathology but misconceptions are preserved by the lack of any disproof. In the material available the complete series of changes observed in gastric mucosa has not been demonstrated. But some evidence for the presence of a similar process is encountered. It is not uncommon to encounter foci where the mucosa is very thin due to the disappearance of Brunner's glands. Here, the mucosa dips deeply to cover this defect and is separated from the muscularis only by a thin layer of lymphoid infiltration and a zone of fibrous tissue. This is compatible with a healed superficial ulceration (Fig. 13).

It should be apparent that equivalent mucosal lesions in stomach and duodenum may produce considerably different effects. The well formed submucosa and thick muscular coat of the gastric wall are capable of concealing

a focal ulcer or cicatrization which in the duodenum will be capable of producing a deformity and interference with motility that might be readily identified by the radiologist. It is common experience in surgery and in surgical pathology that the surgeon resecting a stomach and duodenal bulb is convinced that he has resected a duodenal lesion identified radiologically, but on pathologic examination the presence of a lesion is not confirmed. The usual explanation is that the lesion remains in the inverted duodenal stump, or that it was destroyed in clamping and transection. The lesion sought for has been the typical peptic ulcer involving all coats of the duodenum. It is possible that minimal lesions may be present and overlooked, or ascribed to trauma or artefact.

The terms hypertrophic and atrophic are almost universally applied as descriptive of different types of chronic gastritis. The term hypertrophic is permissible in gross description, for mucosal folds may vary in size and



FIG 13—Healed superficial lesion of duodenal mucosa, with absence of glands

thickness and the mucosa itself may appear to be of increased thickness. The term is frequently used with the implication of hyperplasia. If a grossly thickened mucosa be examined microscopically an increase in the number or size of glands is not found, nor would such a change be expected of glands as highly specialized as those of gastric mucosa. In fact, no elements can be identified in the mucosa which are increased in number or volume beyond that in a section from a corresponding region of the stomach in a specimen not so thickened. The changes are very intimately bound up with edema, but this is of significance in the submucosa rather than the mucosa. The apparent thickening of the mucosa can be explained on a mechanical basis. The mucosa is normally bound to the muscle coat by the loose connective

tissue of the submucosa in such a manner that within a limited range it can be moved from side to side or elevated. If this submucosal space is filled by edema fluid then the fibers of connective tissue assume a more vertical disposition with the result that a given area of mucosa is reduced in size. The result is that the mucosa assumes a crenated pattern and hence appears to be increased in thickness. The term hypertrophic gastritis should be used only as a descriptive term, if at all, and with the realization that it is not an entity with any specific significance.

Atrophic gastritis is an accurately descriptive term, but this is not an entity distinct from the process that has been defined. In the stomach showing an advanced stage of chronic gastritis the repeated focal ulcerations healing with crypt formation result in an increasing loss of glandular elements and those which persist may come to be encountered only in discrete clusters. This is due in part to actual destruction of individual units, but as well to the failure on the part of the germinal epithelium in the neck region, as a result of a prolonged proliferative response, to maintain the rate of replacement of degenerated and disintegrated glandular units. Not only does the specialized epithelium of the gastric glands suffer on this account but, as well, the mucus-secreting elements taking origin from the same germinal epithelium show the results of exhaustion of the regenerative process. In the early stages mucus secretion is diminished. The mucus cells, which were originally tall columnar and filled with a pale mucin displacing the nucleus toward the basement membrane, take on a cuboidal character with a dark homogeneous cytoplasm and a centrally located round dark nucleus. The alteration in character of the mucus-secreting epithelium proceeds from here through metaplasia to the so-called intestinal type, which is marked by cuboidal or low columnar cells, occasionally containing sharply outlined rounded vacuoles of mucin. This alteration occurs first only in isolated patches, but in more advanced cases may come to occur over wide areas or even entirely replace the normal type of gastric mucus-secreting epithelium.

Hyperplasia of the mucus-secreting elements of the gastric mucosa offers a further field for study, but this must be postponed for the time being.

SUMMARY

A detailed study of 213 surgically resected stomachs has revealed a number of changes in gastric glands which at first appeared to be of little significance, but when arrayed in a sequence of increasing severity and magnitude formed an uninterrupted series of lesions that suggest a single disease process. The least of these is the occurrence of scattered glands lined by epithelial cells which are undifferentiated into chief and parietal cells. There are also scattered glands undergoing a process of vacuolar degeneration which is occasionally found to have progressed to complete degeneration with only the ghost of the gland persisting. These changes are thought to be compatible with a normal process of degeneration and repair.

in gastric mucosa. The process of degeneration is sometimes associated with an infiltration by polymorphonuclear leukocytes. This may involve a number of adjacent glands and amount to a focus of necrosis which may border on focal ulceration of the mucous membrane. A lesion of this magnitude can be identified only microscopically.

The minimal lesion which can be recognized grossly is focal ulceration involving only the mucosa. These are round, stellate or linear in type. In the healed state they are grossly identified as a network of shallow fissures with intervening mounds of mucosa which present a pebbled or umbilicated appearance. Microscopically, they appear as crypts in which the surface epithelium dips to the muscularis mucosae, and into which adjacent gastric glands and pits are directed. The even progress of this series of both ulcerated and healed lesions is maintained by ulcerations or scars which may extend through the muscularis mucosae to submucosa, to the muscular coat, or entirely through the muscular coat.

This complete series of lesions is held to be a single disease process to which the term chronic gastritis may be applied. It is described as a process of degeneration or necrosis and repair. When the degeneration and the necrosis are overwhelming, and the mechanism of repair is inadequate, a recognizable peptic ulcer is the result. The element of repair is an essential part of the process. When foci of degeneration and necrosis occur and recur in great numbers a prolonged proliferative response is called forth and exhaustion of the germinal epithelium may occur. This is evident in the atrophy and disappearance of glands and the diminution in mucus secretion or metaplasia on the part of the epithelium of surface and gastric pits.

Hypertrophic gastritis is considered to be a mechanical alteration in the gastric mucosa, but atrophic gastritis is an integral and late stage of chronic gastritis.

CONCLUSIONS

A pathologic process, stemming from the normal degeneration and repair of gastric glands, is outlined and to this the term chronic gastritis is applied.

The imprint of this process can be recognized to a greater or less degree in every surgically resected stomach. Evidence suggesting a similar process has been encountered in the duodenum.

The peptic ulcer, as a lesion of gastric or duodenal mucosa, is not a distinct entity but only the most obvious manifestation of chronic gastritis as here defined.

The symptomatology of the peptic ulcer may be present in the absence of a grossly demonstrable lesion but can be explained on a basis of chronic gastritis.

The apparent greater frequency of duodenal over gastric peptic ulcers may be due to the fact that minimal lesions can more readily produce a recognizable deformity in the duodenal wall.

PROTEIN METABOLISM AND BED SORES*

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THE SUBJECT OF DECUBITUS ULCERS or bed sores has received but cursory treatment in current textbooks on medicine and surgery. Present-day standard medical texts such as Cecil's,¹ and Christian's revisions of Osler,² merely refer to the occurrence of bed sores in some diseases of the central nervous system and in such debilitating diseases as typhoid fever and diabetes. Homan's³ textbook of Surgery mentions debilitating diseases and poor nutrition of the skin as contributing causes in addition to local pressure. Cole and Elman⁴ state "Any poorly nourished patient suffering from prolonged and debilitating illness, as typhoid fever, tuberculosis, *etc.*, may develop bed sores unless adequate nursing care is exercised in turning the patient and protecting bony prominences."

Freeman,⁵ writing in Keen's "Surgery: Its Principles and Practice" in 1919, under the chapter on mortification or gangrene, gave the subject a fairly extensive treatment. A comprehensive list of the usual sites was given, and the sores were divided into ordinary and decubitus accompanying lesions of the central nervous system. The etiology of ordinary bed sores was attributed to probable thrombosis of the smaller veins of the region, giving rise to gangrene, sloughing and ulceration. Other factors mentioned as more or less important were (1) Hypostasis, (2) lack of tissue resistance caused by disease, weakness and defective metabolism, (3) alteration in vascular intima due to bacterial poisons, lack of nutrition from capillary stasis, changes in blood, *etc.*, and (4) evaporation of fluids from the tissues. It was also implied that local pressure injury was usually the immediate etiologic factor. Thus, there has not been much new added to the knowledge in the etiology of bed sores from 1919 to date. Exception, however, must be made of Joseph⁶ who, in 1930, used insulin to improve the "general condition of the patient," and of McCormick,⁷ who, in 1942, postulated that bed sores were caused by avitaminosis B.

Throughout this brief survey of the literature there runs the implication that malnutrition somewhat contributes to the development of bed sores. The therapy, however, except for McCormick's use of vitamin B, seems to make no provision for the improvement of nutrition. The principal measures may be briefly reviewed.

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- 1 Relief of local pressure
 - All mattresses
 - Rubber rings
 - Frequent turning
 - Sawdust beds⁷
- 2 Local stimulation
 - Light massage
 - Sunlight
 - Infra-red radiation
 - Ultraviolet light radiation
- 3 Stimulation of healing with dressings of
 - Balsam of peru
 - Cod liver oil
 - Gentian violet
 - Tincture of benzoin
- 4 Antiseptics
 - Chlorine and other compounds
 - Sulfonamides

Our interest in this condition was aroused by a case of extensive third degree burns who was losing so much protein from the burned areas that during the second week of his stay in the hospital, in spite of repeated plasma and blood transfusions, his total plasma proteins were 5.4 Gm %. At this point he developed a bed sore over the sacrum. This occurrence suggested a possible relationship between hypoproteinemia and the development of bed sores. Accordingly, total plasma protein determinations were taken in 35 random cases of bed sores. The results with correlative data are given in Table I.

TABLE I

PLASMA PROTEIN CONCENTRATION AND OTHER CORRELATIVE DATA IN 35 CASES OF BED SORES

Ages Ranged from 30 to 81 Years, Nutritional States from Poor to Emaciated

T P Ranges Gm %	No of Cases	Ranges of Hematocrit Values	Description of Bed Sores
Above 6 40	0		
5 0 —6 35	6	42—44	All * sim (4 Psych 2 Frac)
5 5 —6 00	12	39—42	5* 7** 8 sim 4 mult (9 Frac 3 Psych)
5 0 —5 5	12	20—42	4* 8***, 5 sim 7 mult (2 Psych 4 Frac 6 Gen)
4 0 —5 0	3	20—39 5	1** 2****, all mult (1 Frac 2 Gen)
3 75—3 8	2	15—22	1**, 1****, both mult (both in Gen Wd)

Key

* = Under 1 cm in diameter
 ** = From 2 to 5 cm in diameter
 *** = From 5 to 10 cm in diameter
 **** = Over 10 cm in diameter

Psych = Psychiatric Ward
 Frac = Fracture Ward
 Gen = General Ward
 Sim = Simple
 Mult = Multiple

It will be seen from Table I that all the cases had poor nutritional states, and that none of these 35 cases had a plasma protein concentration over

6.35 Gm % Six cases had plasma protein concentration of between 6.0 and 6.35 Gm %, a range which may be called the upper limit of abnormal, and the other 29 cases were below 6.0 Gm %. If the severity of the sores is now analyzed against the level of plasma proteins it will be seen that the extent and depth of the ulcers as well as the multiplicity seem to be related to the level of plasma proteins. It is also interesting that in the group of six with plasma protein ranges between 6.0 and 6.35, four were in the psychiatric ward and two in the fracture ward, and of the 12 in the plasma protein range of between 5.5 to 6.0, nine were in the fracture ward and three in the psychiatric ward, while none of the 18 in these two groups belongs to the general wards, and that all the cases from the general wards occurred in the groups below the plasma protein ranges of 5.5 Gm %. The significance of this distribution will be commented upon later.

From the study of this table alone there seems to be a strong probability of a relationship between bed sores and hypoproteinemia.

One of the patients (p.p. 6.15 Gm %) in the first group and one in the third group (p.p. 5.76 Gm %) were placed on a high protein diet. The healing of the ulcer and the improvement in general condition were so prompt and definite that it was decided to undertake a controlled study of the nitrogen balance of a series of patients with bed sores, first under the usual ward feeding and then after they were placed on adequate caloric and nitrogen diet. Eight cases were embraced in this study.

EXPERIMENTAL CONSIDERATIONS

Nutritional Regimens—Two of the eight patients for the first six days of study were placed on high caloric but low nitrogen diet. Table II is the protocol of one of these patients. The other six had a control period of the first three days during which the usual ward diets were given. The caloric and nitrogen figures were taken by subtracting the approximate values of food unconsumed from the values given for the diet as it appeared in the dietitian's charts. After these control periods the patients were given an amino-acid dextrose mixture* of homogenous composition dissolved in 500 cc physiologic saline solution and enough water to make the mixture easy to administer. The patients were thus taking approximately 4.5 Gm of NaCl daily. The water intake was unrestricted. When appetite returned, it was sometimes necessary to supplement the mixture with an egg sandwich, the caloric and nitrogen values of which were also calculated from the dietitian's charts. Tables III and IV are protocols representative of this group of six. During the entire hospitalization period all these eight patients had been receiving daily, by intramuscular injection, for a period of from 4 to 12 weeks, thiamine chloride 30 mg, nicotinic acid, 50 mg, and cevitamic acid, 100 mg.

* This mixture was kindly prepared for our use by Frederick Stearns & Company, Detroit, Michigan.

Collection and Care of Laboratory Samples—The urine was preserved with thymol, kept in the refrigerator, and pooled over each 72 hours. The urinary output ranged from 850 to 1250 cc. The feces of each patient were collected in two pooled specimens—one for the control and the other for the feeding periods. They were kept in sulfuric acid.

The hematocrit was usually determined each time the total plasma protein concentration was determined by the Barbour-Hamilton⁸ method. When it was desired to determine albumin and globulin figures, the method of Wu and Ling, as modified by Greenberg,⁹ was used. In determining the nitrogen of the urine and stools, the method of Rappaport, as modified by Levy and Palmer,¹⁰ was used.

Weights of the Patients—All the eight patients except one (D P, Table II) were weighed periodically during the period they were under study. Bedridden patients were placed on a tared stretcher and the loaded stretcher was then weighed on two Howe platform scales, the two front wheels resting on the platform of one scale and the two hind wheels on that of the second. From the combined weight of the stretcher and patient was subtracted the weight of the stretcher, leaving the patient's weight. The sensitivity of each scale was 25 Gm, so that the sensitivity of the two-scale system was approximately 50 Gm.

Two of the cases had copious discharges, one from the bed sore itself (B M, Table III), and the other from an unhealed amputation stump (Figure 4). The 24-hour discharges were collected on filter papers of predetermined weight and nitrogen content and then analyzed for total nitrogen, using the same chemical method as in the urine and stool determination. This source of nitrogen loss was also included in the figures for total nitrogen output.

EXPERIMENTAL RESULTS

The general results of the eight cases are so strikingly uniform that only three protocols need be given, each illustrating a point under investigation.

Table II (J R) embodies the findings of a case of simple and mild bed sores complicating fractures. He was one of the two cases who, during the first six days, were put on a high caloric but low nitrogen diet. He registered throughout these six days a negative nitrogen balance, a loss of weight, a slight depression in the plasma protein concentration, and no improvement in the ulcers. On the seventh day both of these patients were placed on a high caloric and high amino-acids diet with a resulting positive nitrogen retention. A gain in weight, an upswing in the plasma protein concentration took place, and healing became perceptible on the fourth day after the high protein diet was started. The hematocrit values remained relatively unchanged throughout the course of the work.

Table III represents the nitrogen balance studies of D P who, as a result of impaired appetite and diarrhea, following an operation for repair of a traumatic rupture of the sigmoid, was in a poor nutritional state. The

PROTEIN METABOLISM AND BED SORES

TABLE II

J R, MALE AGE 56, ADMITTED 7-13-42, FRACTURE UPPER RIGHT FEMUR, BED SORE 5 WEEKS, SLOWLY ENLARGING

Date	Caloric Intake	N Intake Gm	N Output Gm	N Balance Gm	Hemato-crit	P Gm	P %	P Alb Gm %	Wt Lbs	Description of Bed Sores	
Sept 6-7					41	6	2	3	3	102 5	Over sacrum, 1 cm , sluggish, greyish base, involves subcutaneous tissue
7-8	9300	18	22 6	—3 3							
8-9											
9-10											
10-11	9300	18	21 25	—3 25	40 5	5 9			99 25	No improvement	
11-12											
12-13											
13-14	8420	48 6	31 42	16 58					102	Base pink granulations forming	
14-15											
15-16											
16-17	9165	52 45	31 74	20 71	395	6 2			106 5		
17-18											
18-19											
19-20	9165	52 45	35 3	15 15	40	6 6			110	0 5 cm in diameter	
20-21											
21-30	3800 daily	25 daily			41	6 9	4 1	115	Healed on 9/30		

presence of edema consequent to a total plasma protein concentration of 4.6 Gm % made it useless to follow the weight curve. During the first three days (*i.e.*, October 7-10) the patient's caloric and nitrogen intakes were calculated from the portions of the prescribed diets which he consumed. He lost 1.02 Gm of nitrogen during these three days. During the subsequent nine days he was given the amino-acid-carbohydrate mixture described above, with the result that he was on a positive balance daily. Signs of healing were definite on the fourth day, and the ulcer, which was initially superficial, was healed on the ninth day. It will be noted that the hematocrit did not change materially during these days, the slight fall being perhaps due to increased blood volume as a result of a higher plasma protein concentration.

TABLE III

D P, MALE, AGE 61, ADMITTED INTO KING'S COUNTY HOSPITAL 8-9-42, WITH DIAGNOSIS OF TRAUMATIC RUPTURE OF RECTOSIGMOID OPERATION FOR CLOSURE OF PERFORATION BED SORES BEGAN 9-10-42

Date Oct	Caloric Intake	N Intake Gms	N Output Gm	N, Balance	Hemato- crit	P P Gm %	P Alb Gm %	Description of Bed Sores
7- 8 } 8- 9 } 9-10 }	3386	22 4	33 42	—11 02	22	4 6	2 8	Sacral, 4 cm involves dermis No signs of healing, edema of ankles
10-11 } 11-12 } 12-13 }	9300	64 8	42 94	+21 86				
13-14 } 14-15 } 15-16 }	9300	64 80	35 04	+29 76				
16-17 } 17-18 } 18-19 }	9300	68 80	41 2	+27 8	20	5 3		
					19	5 9		Ulcer almost healed

Table IV represents a patient (B M) whose bed sore was exceedingly severe, in area as well as in depth The pictures in Figure 1 represent different stages of healing As in the other cases, signs of healing were definite on the fourth day after the nitrogen balance was reversed from negative to positive The plasma proteins and the body weight both underwent a corresponding rise The original ulcer was so extensive that the first day's discharge contained 893 mg of nitrogen, corresponding to the loss of almost 5.56 Gm of protein, or 113 cc of plasma of the protein concentration of that day

TABLE IV
B M MALE AGE 41, ARTERIOSCLEROTIC GANGRENE OF RIGHT FOOT
AMPUTATION AT KING S COUNTY HOSPITAL 6-11-42 BED SORE'S BEGAN 8 15-42

Date	Caloric Intake	N Intake Gm	N Output Gm	N Balance Gm	Hemato crit	P Gm	P %	P Alb Gm %	Wt Lbs	Remarks Description of Bed Sore
Oct										
7- 8	2700	16 8	32 375	-16 375	34	4 9	2 2	94		9" x 6" x 1" Dirty greyish sloughing base, necrotic edges
8- 9										
9-10										
10-11	9300	64 8	42 73	+22 068						
11-12										
12-13										
13-14	9300	74 9	35 761	+39 139						Base cleaner, granulations forming
14-15										
15-16										
16-17	9300	78 9	36 8298	+42 07					995	
17-18										
18-19										
19-20	9300	78 9	44 826	+34 072	36	5 42	2 7			
20-21										
21-22										
22-23	9300	78 9	37 8	+41 1					104	Healing rapid 7" x 5" x 3/4"
23-24										
24-25										
25-26	9300	78 9	51 166	+20 73						
26-27										
27-28										
28-29	9300	78 9	42 276	+33 624						
29-30										
30-31										
					36	5 82	3 2	115 5	5" x 4" x 1/2"	

In Figure 1 are photographs of different stages of healing of this patient The wound healed rapidly at first but lost momentum, and it took almost three months to effect a complete healing of this ulcer which was initially 9 x 7 x 2 inches

Figures 2 and 3 show the stages in the healing of two other patients whose protocols are not shown here but whose healing followed the usual pattern of being visibly definite three or four days after the nitrogen balance was reversed from negative to positive Figure 3 also shows an amputation stump which evinced no healing when the bed sore developed, but which began healing as soon as the bed sore showed signs of healing

COMMENT AND DISCUSSION

This study may be said to have gone through three stages The suggestion given by the development of bed sores in a case of burns, with

1a



1b



1c



1d



FIG 1—Panel 1a shows the ulcer of patient B M, Table IV, in the original state. Note the greyish, necrotic base and edematous granulations. Panel 1b shows the ulcer one week after nitrogen balance was reversed from negative to positive, and maintained. Note the healthier color. Panels 1c and 1d show the ulcer during, respectively, the 6th and 12th weeks.

21



2b



2c



FIG 2—Panel 2a shows the original bed sore, undermined, livid, and glistening with edematous granulations, and with no tendency to heal. Panels 2b and 2c show the state of the ulcer three and six weeks after maintenance of nitrogen balance. Note the pink, healthy granulations in both panels.



FIG. 3—Panels 3a and 3b show, respectively, the original sore and the unhealed amputation stump. In the latter note the necrotic edges, the greasy exudate, and the livid and glistening tissue. Panels 3c and 3d show, respectively, the healed ulcer 12 days after treatment, and the healing amputation wound.

hypoproteinemia became a probability when the plasma protein concentrations of a series of 35 cases were determined and correlated with the severity of the ulcers, and when a high protein diet was found to cause healing in the only two of these 35 in whom high protein diet was instituted. The probability was confirmed by the controlled nitrogen balance studies of eight patients with bed sores.

The failure of the ulcer to heal with high caloric and low nitrogen diet for six days in two cases, as represented by J R (Table II), and the occurrence of signs of healing on the fourth day after the nitrogen balance was made positive showed that it was not high caloric intake which initiated the healing. The use of a mixture which contained no fat indicated that fatty acids are not essential in the healing of these sores, which was implicated. The narrow ranges in which the hematocrit changed during the study period and the fact that D P (Table II) had a hematocrit of only 22 throughout the healing period indicated the lack of direct relationship between anemia and the development of bed sores. The vitamin therapy to which these patients were subjected through their hospital stay, prior even to the development of bed sores, indicated that in the presence of hypoproteinemia, vitamins do not prevent the development of bed sores. Finally, the prompt healing becoming evident four days after protein anabolism was achieved points to a definite relationship between protein metabolism and the development of decubitus ulcers.

At this point, it may be pertinent to state the rôle of protein nutrition in the causation of bed sores. It is known that a certain amount of pressure applied locally to even a normal tissue for a sufficient length of time can cause necrosis of that tissue. In patients with protein malnutrition the tissues are so changed in character that it apparently takes a smaller amount of pressure, or the same amount of pressure for a shorter length of time, to cause tissue necrosis. It may also be expected that when the malnutrition reaches a certain point even the amount of pressure exerted by the recumbent body for the usual period of rest may cause tissue necrosis.

This combination of pressure and of tissue of "a changed character" in the causation of bed sores explains the distribution of the 35 cases in Table I in the fracture, the psychiatric and the general wards. In the psychiatric ward all the patients had large doses of hypnotics, which constrained the patients to lie unconscious in one position for a long time. In the fracture cases this same constraint was exerted by a plaster encasement. Meanwhile the loss of nitrogen from the body, either as a result of "toxic loss" due to the injury, or as a result of undernutrition, or of the combination of both, alter the character of the tissues. In the general ward, however, the patients were able to change positions more freely and thus would not develop sores until malnutrition was more marked.

This same hypothesis of combined causation would also explain the

fact observed by Cushing¹¹ that marasmic infants develop bed sores on the back of the scalp, since in the infant the head is perhaps the heaviest part of the body

Abbott and Mellors' observations¹⁶ that a patient with several decubiti healed rapidly after anabolism was achieved by sufficient caloric and protein intake and that several similar patients also healed rapidly when given repeated plasma transfusions are consonant with this hypothesis

Apart from the light which this study throws on bed sores, the implication that tissues of patients with poor protein nutrition have this character of impaired viability is significant in connection with the entire problem of protein nutrition. It has previously been shown that tissues of hypoproteinemic individuals have impaired healing powers,^{12, 13, 14} and Altshuler, *et al*¹⁵ have recently shown that intractable surface ulcers heal in response to amino-acid therapy

Whether the same causative factors are also operative in bed sores occurring in cases of transverse myelitis, and other diseases of the central nervous system, remains for further study. The favorable response obtained by McCormick in his one case to improved nutrition suggests a similar etiologic factor

SUMMARY AND CONCLUSIONS

1 In 35 random cases of bed sores, it was found that the plasma protein concentration were invariably below the lower limits of normal

2 In a controlled study of two other cases it was found that the giving of a high caloric diet resulted in further weight loss to the patient, in a negative nitrogen balance throughout the six days, in a depression of the plasma protein concentration, and in no improvement in the condition of the sores

3 In six other cases it was found, during a control period of three days, that the diets they were taking in the wards resulted in a negative nitrogen balance, a slight loss of weight, and lack of improvement of the ulcers

4 In all the eight cases there was improvement in the general condition, gain in body weight (except D P in whom the weight was not followed), a rise in plasma proteins, and healing of the ulcer when the nitrogen balance was reversed from negative to positive

5 Fatty acids are not essential to the healing of bed sores, and in the presence of protein deficiency vitamins do not seem to prevent the development of bed sores

6 The theory is advanced that both local pressure and a tissue of impaired vitality as a result of protein deficiency are factors in the causation of bed sores

Grateful acknowledgment is made to Dr Irving Barcham and to the Hospital for Joint Diseases, New York, for contributing two of these cases

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SAPHENOUS (LIGATION) RESECTION IN THE OBESE*

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DURING RECENT YEARS the surgical literature has contained numerous and excellent accounts of the treatment of varicose veins and their complications. In order to avoid unnecessary repetition this paper will be limited to a discussion of only two factors. First, causes for the deaths reported in the literature following saphenous resection, and, second, the reasons for failure to ligate all the collateral branches in the fossa ovalis. This discussion is based on an experience with 418 consecutive personal cases (the majority of whom were obese) in which a high saphenous resection was performed, either for phlebitis or for varicose veins. In this discussion the term saphenous resection is used instead of ligation, inasmuch as the operation advocated today is no longer a simple ligation of the saphenous vein, but rather a resection of a portion of the proximal end of the saphenous vein together with the collateral superficial venous circulation in the fossa ovalis. There were no deaths in this group, and the incidence of recurrences is growing smaller each year, due we believe to careful attention to the details to be discussed.

A review of the literature might impress the reader with a number of facts. The mortality rate seems to be proportional to the number of patients who are kept in bed. Moore and Knapp reported 121 cases treated at the New York Hospital, with two deaths from pulmonary emboli. Both of these patients were kept in bed. Dean and Dulin reported two deaths from emboli, each case being kept in bed ten days after injections. Weeks and Mueller, reporting on 325 cases treated on the First Surgical Service at Bellevue Hospital, described one death following bed rest of eleven days.

Faxon, Oschner, and others have emphasized the need for keeping these postoperative patients up and about. Our own experience has borne this out.

Although the cause of thrombophlebitis or phlebothrombosis is not known, most writers believe that any factor which slows the venous return from the leg is an important contributing factor. Inasmuch as this circulation is largely dependent upon the muscle contraction of the legs and diaphragm, patients at bed rest have a sluggish venous flow and are more likely to develop a soft, non-adherent thrombus whose release may cause a fatal embolism.

If the surgeon recognizes the need for allowing his patient to be up and about immediately after the operation has been performed, he will refuse to treat any case where he is not reasonably sure that this can be accomplished. The common causes of failure might be listed as follows:

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SAPHENOUS VEIN RESECTION

- 1 Nausea and vomiting from morphine
- 2 Postoperative pain
 - a Due to trauma of the tissues in the operative wound
 - b Due to a thrombophlebitis from injections given at the time of operation
 - c Due to infection
- 3 Pain from an active thrombophlebitis for which a high saphenous resection has been performed
- 4 Weakness, due to the fact that the patient has been kept in bed during the preoperative period for the care of an open varicose ulcer

We have been impressed with the large number of patients who were nauseated by morphine. This is sometimes not recognized, as the vomiting is attributed to the anesthesia. Before discontinuing the use of morphine in patients who had a high saphenous resection, about two out of ten cases had difficulty immediately after the procedure due to nausea.

If the operation is performed with a minimum amount of trauma, there should be little postoperative pain. In this series of cases, catgut, silk, plastigut and cotton have all been employed and the latter has been found to be the most satisfactory because it appears to cause less tissue reaction and is not extruded from infected wounds.

We have entirely given up the practice of injecting the saphenous vein at the time of its resection and have been interested to note that many others working on this problem have come to this same conclusion. Our reasons might be listed as follows:

- 1 The pain of the thrombosing vein might be responsible for preventing the patient becoming ambulatory at once.
- 2 In some instances the saphenous vein will thrombose spontaneously after its ligation. This is particularly true when ligation has been done at several levels.
- 3 The varicosities will frequently contract following ligation so that the resulting thrombosis obtained after subsequent injections will be smaller than if the injections were given at the time of the operation.
- 4 As has been pointed out by Atlas, retrograde injection at the time of operation may give rise to a deep thrombophlebitis.

The problem of infection will be dealt with in a description of the operation. It suffices to say that experience has confirmed what others have said before, "never perform a high resection of the saphenous vein in the presence of an open lesion on the leg." When necessary we have hospitalized these cases, and after the lesion has been cleaned up, healed or grafted when indicated, the patient has been allowed out of bed for a few days, before the operation is performed. At such times a firmly fitting elastic bandage is worn. We believe it is a mistake to take any patient to the operating room for a saphenous resection who has been kept in bed for the treatment of a varicose ulcer, even though the patient is expected to be out of bed immediately after the operation.

Experience has shown that the most important single cause for the recurrence of varicose veins is the surgeon's failure to ligate all the collateral branches in the fossa ovalis. We believe that most surgeons realize the need for performing this step in the operation and that the real cause for failure is due to the fact that they find the higher branches inaccessible through their incision, especially in the obese. Ochsner and Mahorner recognized this fact and advised the use of a vertical incision crossing the



FIG 1 —A photograph showing recurrent varicosities occurring in a male five years after a "high saphenous ligation" where the vein was divided several inches below the saphenofemoral junction. Following a secondary operation at a higher level these varicosities thrombosed spontaneously.

flexion crease of the groin. We have tried this with poor success. This incision is made at right angles to the lines of cleavage in the skin which in itself causes an unsightly scar. Again, the operation must necessarily be performed on many obese patients where such an incision crosses the apron of fat which hangs down over the inguinal region and increases the difficulty of the procedure. The amount of motion in such a wound is greater than in a transverse incision and in itself may be a factor contributing to poor

wound healing Realizing the vital need for satisfactory wound healing in this type of case, we returned to the transverse incision

Most writers describe the transverse incision as being made "parallel to Poupart's ligament" or "parallel to Poupart's ligament and just below the flexion crease" It is our opinion that as long as such incisions are routinely made on the obese, the collateral branches in the fossa ovalis will not be adequately ligated in many instances Recent writers have been impressed with the fact that the saphenofemoral junction lies much higher than they expected This has been borne out in the experience with the present series Various land marks have been cited to aid the surgeon in outlining his incision Some operators suggest that the femoral artery may serve as a landmark, others refer to Poupart's ligament, some to the flexion crease in the groin, and still others to the pubic spine We have found that in the obese women the femoral artery may be palpated with difficulty, that Poupart's ligament is not easily outlined in the obese, the flexion crease is a variable anatomic landmark but that the pubic spine is a constant point which can usually be palpated even in a heavy patient The fact remains that little has been said about the distance from the flexion crease of the groin to Poupart's ligament Surgeons unconsciously find themselves draping the patient with reference to the flexion crease rather than to Poupart's ligament We have found that in very obese patients it has been most difficult to reach the saphenofemoral junction through incisions placed at or below the flexion crease itself Hanging below Poupart's ligament is a thick, redundant fold of fat which in many instances may even overlap the thigh The flexion crease in such an instance acts as a constrictive sling which prevents the operator from reaching the level of the highest branches under the superior wound margin In the thin individual this is no problem, but any incision which is so limited in its application is unsatisfactory We believe that for these reasons the efforts of many surgeons working on obese patients are defeated Often all accessible branches are ligated and the wound closed without the saphenofemoral junction being actually visualized This has certainly been the experience of the writer and of those handling the cases admitted from the Varicose Vein Clinic, until the higher placed incision was employed in the obese Faxon, in 1934, described a death following a high saphenous resection and included the comment made by the operating surgeon "Because of the great amount of subcutaneous fat, he could not demonstrate the saphenofemoral junction"

For these reasons we began making a transverse incision above the flexion crease of the groin on all obese patients, raising or lowering the level above the crease, depending upon the amount of fat present With this new approach we were surprised to find how high the upper branches lie above the flexion crease This higher approach brings the surgeon down on the branches first and as these are isolated and ligated, the saphenous vein is gradually mobilized Such an incision keeps the wound on top of

the fatty apion and away from the skin maceration which is so common in this type of patient

Wound complications constitute a definite hazard in this operation. This is not difficult to understand when we consider that so many factors are present which may contribute to poor wound healing. The incision is made in a hair bearing area where there is apt to be considerable perspiration. The wound is not kept at rest as it is imperative that the patient be ambulatory. The operation is carried out almost entirely in fatty tissue which has a low resistance to infection. Because of these facts, we have felt that no type of wound deserves more careful attention to detail, as an infection may mean a bedridden patient and subsequent death from an embolus. In this series of 418 cases there has been a two per cent incidence of wound infections. Of this group, it was only necessary to hospitalize four cases (one per cent) because of infection.

OPERATIVE TECHNIC

The present operative procedure includes all details which might in any way help to lower the incidence of wound complications.

After the usual skin preparation, the towels are so placed that an incision can be made in an obese patient from a quarter of an inch to an inch above the flexion crease of the groin, two and one-half to three inches in length. The level of the incision, of course, depends upon the amount of fat in this area. The pubic spine is found to be the most reliable landmark in placing the upper towel. Under local anesthesia, these towels are then sutured to the skin with fine cotton on cambric needles. The incision is then carried down through the skin and immediate subcutaneous fat. The bleeding points are clamped with small mosquito hemostats, as it has been found that the ordinary hemostat will pull off of these small vessels because of its weight. The bleeding points are ligated with fine cotton, usually No. 70. At this point, skin towels are clipped to the wound margins with Michel clips, care being taken not to squeeze these clips so that they might traumatize the skin margins. Having thus redraped the field, the dissection is carried down through the deeper subcutaneous fat and fascia. As soon as clamps have been placed on three or four small bleeding points they are ligated at once as it is important to keep the wound free of instruments. In our opinion, any bleeding point deserves ligation as the field must be kept meticulously dry.

The dissection next brings the operator down on a group of lymph nodes which will vary in size, depending on whether or not there have been open lesions on the leg during previous years. These are best dislocated upward *en masse*. The saphenous vein is usually found immediately under these lymph nodes or just medial to them. In many cases the superficial iliac vein is first encountered descending obliquely through the fat above the upper border of these lymph nodes to join the saphenous. This vein at times may serve as a guide to the location of the saphenofemoral junction.

SAPHENOUS VEIN RESECTION

The remaining collateral branches are then carefully dissected out from their surrounding fat and divided by slipping an aneurysm needle under them and ligating the vein with fine or medium cotton, depending upon its size (fine cotton No 70, or medium cotton No 36). We believe that the use of the aneurysm needle with division of the vein between ligatures is superior to dividing the structure between clamps, inasmuch as the clamp crushes and devitalizes a small portion of the tissue. Again, in handling

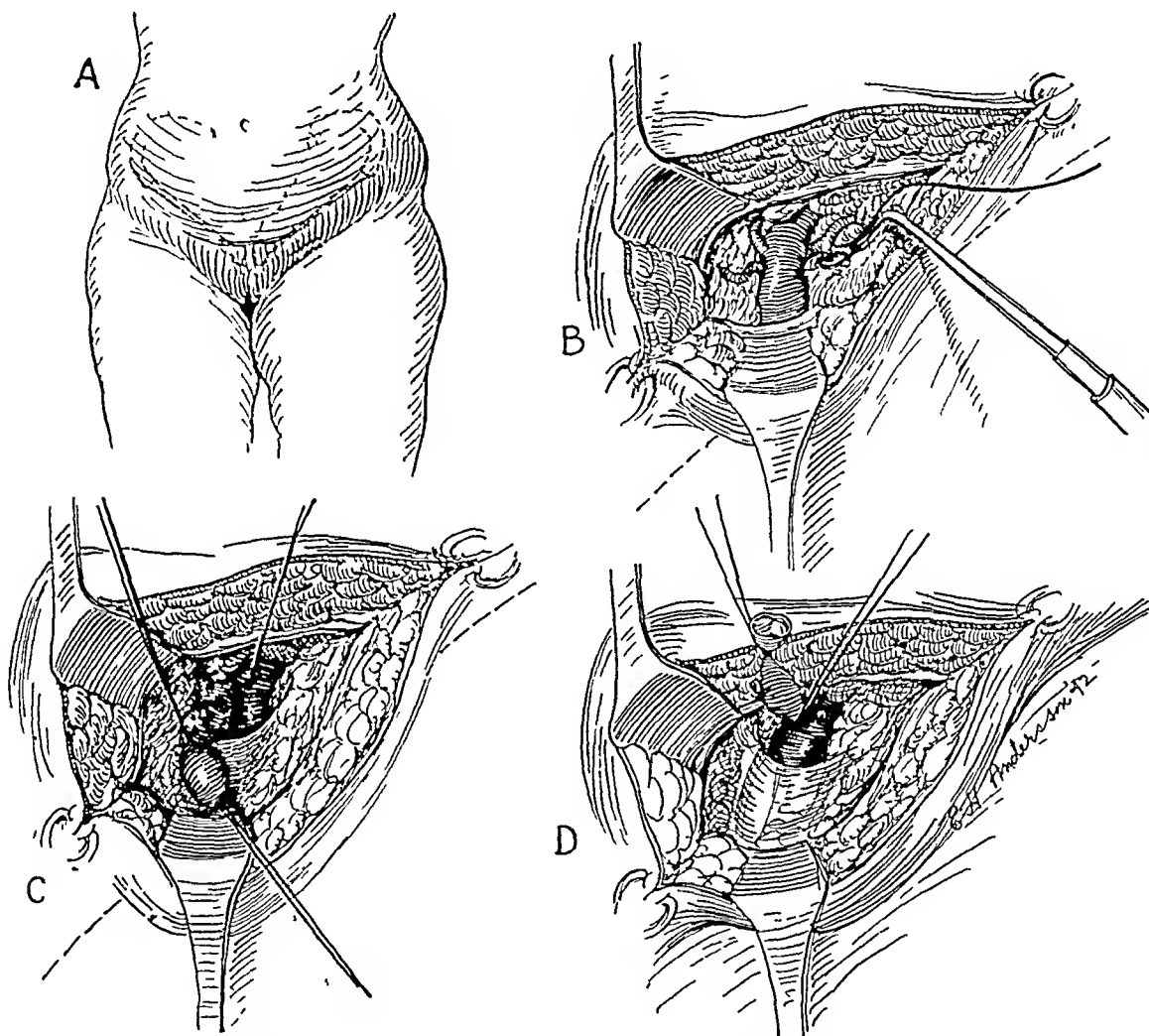


PLATE I—A Indicates the protruding rôle of fat between Poupart's ligament and the flexion crease of the groin. The incision should be placed above the crease.

B The dotted line represents the flexion crease of the groin. The drawing illustrates how far above this level the branches in the fossa ovalis appear in the obese.

C The saphenous vein has been doubly ligated with cotton and all but one collateral branch has been divided. A portion of the femoral vein is seen at the saphenofemoral junction.

D The saphenous vein has been divided and the proximal stump is elevated while a ligature is being placed at the saphenofemoral junction. Note how high this ligature must lie above the flexion crease of the groin.

the clamps the friable veins may be torn. Tissues divided between ligatures do not always become necrotic but pick up a new blood supply when returned to their original position in the wound.

In this manner the field is never obscured with a number of clamps and should a small vein be inadvertently damaged, the bleeding can be quickly controlled as the field is not obstructed. At times it has been noted that the lateral superficial femoral vein is larger than the saphenous

itself As the branches are divided between ligatures, the saphenous vein is mobilized and can be dissected free from the underlying fascia Great care must be taken not to injure the pudendal artery which usually passes under the saphenous vein at this point but in some instances may pass directly above it

Following immobilization of the saphenous vein, at this point a two-inch segment is resected between ligatures of medium cotton and the proximal stump elevated into the wound As it is freed-up by sharp dissection, the femoral vein is visualized lying just under the deep fascia of the leg It is now possible to place one or two cotton ligatures about the stump, flush with its junction with the femoral vein The redundant vein that was elevated in the wound is then excised The superficial fascia is closed separately with interrupted sutures of fine cotton The skin towels are then removed and the wound closed with interrupted end-on mattress sutures of fine cotton We have found that in many patients the skin is thin and tends to invert For this reason the end-on mattress suture has been used routinely even though it requires a few additional minutes to insert

The usual operative time is between 35 and 50 minutes, depending upon the size and weight of the patient The operation performed today takes about 15 to 20 minutes longer than the operation performed five years ago, due to the demonstrated need for including the details previously mentioned Formerly, we performed a bilateral ligation at one time However, during the last two years we have again found that patients are more easily kept ambulatory if one side is operated upon one day and the second side the following day As has been mentioned before, these patients are given no morphine but are given a barbituate one hour before coming to the operation room Following the high saphenous resection, incompetent communicating branches of the short saphenous vein are ligated when indicated

CONCLUSIONS

Any factor such as nausea, weakness, or pain which prevents the post-operative patient from remaining ambulatory increases the risk of a high saphenous resection (ligation)

Any incision made parallel to and below the flexion crease of the groin will prevent the operator from successfully ligating all collateral branches on all obese patients

This paper summarizes the experiences gained from a series of 418 cases of high saphenous resection, the majority of whom were obese There was no mortality, and an incidence of two per cent wound infection

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CARCINOMA OF THE BREAST

II—CRITERIA OF OPERABILITY (CONTINUED)

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EDEMA OF THE SKIN

EDEMA OF THE SKIN over the breast is an exceedingly important sign of the extent of breast carcinoma, the significance of which is not generally recognized by surgeons

It was first described by French surgeons almost a century ago Lannelongue⁵ gives the great surgeon and surgical pathologist, Auguste Nélaton, the credit for originating the apt descriptive term "*peau d'orange*" that has kept its place in medical nomenclature through the years Figure 1 illustrates this striking appearance

Sir William Banks,^{6, 7} a distinguished Liverpool surgeon, who was one of the pioneers during the last quarter of the 19th century in emphasizing the necessity for radical surgical attack upon breast carcinoma, compared the appearance of such edematous skin to saddle leather, and called it "pig-skin" He offered the explanation that the fine points in its surface are "the hair follicles caught and tucked down by the cancer" His contemporary, Thomas Bryant,⁸ of Guy's Hospital, who, in 1887, published a little book on diseases of the breast, which was the best thing of its kind that had been done up to that time, preferred the term *edema* of the skin He pointed out that such edema is one of the features of a particularly malignant form of breast carcinoma which he called "acute edematous infiltration of the skin and breast" or "brawny infiltration" His description of this form of the disease, which today has come to be called the *inflammatory type* was an excellent one, and was illustrated with a colored drawing

Although Bryant was a skilled clinician he was not much of a microscopist Indeed, his understanding of the pathologic processes involved in the spread of breast cancer was rudimentary He did not understand the mechanism of metastasis by tumor emboli, and conjectured that carcinoma spread by what he called "infection" that is "the acquired power possessed by morbid epithelial cells, when coming into contact with embryo undeveloped cells, of influencing their development, and causing them to take on the epithelial form"

Bryant was writing in terms of gross pathology when he wrote regarding the acute "brawny infiltration" form of breast carcinoma "These local symptoms are always associated with rapidly progressing disease, in which the original nidus not only spreads rapidly by infiltration, or 'local infection' but also by 'lymphatic infection,' the lymphatics, as described, being apparently filled, if not choked, with the epithelial material which it is conveying

to the lymphatic glands” This observation of Bryant’s was certainly an astute one, even though it was not based upon microscopic studies, and should not be interpreted as an explanation of the microscopic changes responsible for skin edema

The first to study the phenomenon of skin edema from the microscopic point of view was Archibald Leitch⁹ During the years he spent at Middlesex he became interested in the problem of acute mammary cancer and he made

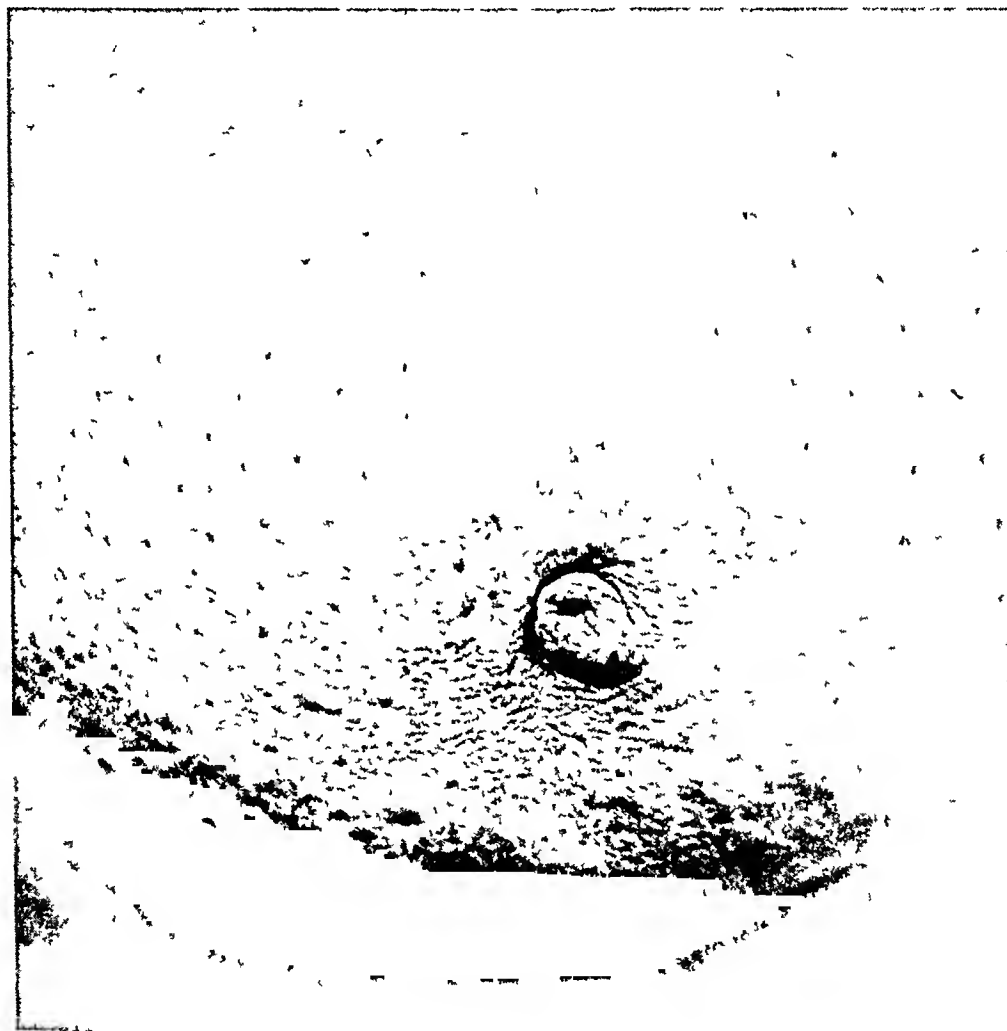


FIG 1 —Close up view of edema of the skin over the breast

sections of the skin in several cases in which there was extensive edema of it He saw that the corium was enormously thickened by edema The arterioles were dilated, and many were filled with cancer cells There was a marked perilymphatic infiltration of lymphocytes and plasma cells Leitch described these findings in a paper published in 1909 entitled "*Peau D'Orange* in Acute Mammary Carcinoma Its Cause and Diagnostic Value" He concluded that the cancer cells had permeated the skin lymphatics in the opposite direction of the lymph stream, blocking the lymphatic circulation of the skin and causing edema of it The depressions in the edematous skin were the exaggerated pits of the hair follicles

Recent writers on inflammatory carcinoma of the breast, such as Taylor and Meltzer,¹⁰ have accepted Leitch's interpretation that its essential feature

is a subepidermal carcinomatous lymphatic permeation. The disease has come to be fairly well known to surgeons as an extraordinarily malignant form of breast cancer, which is recognizable by the generalized enlargement of the breast and the extensive redness and edema of the skin over it.

No one, however, has given special attention to the phenomenon of edema of the skin in itself, and to its prognostic significance. It is not generally appreciated that this important clinical sign is seen in the later stages of all forms of breast carcinoma, whether they be rapid or slow in growth rate. These are the features which we wish to emphasize.

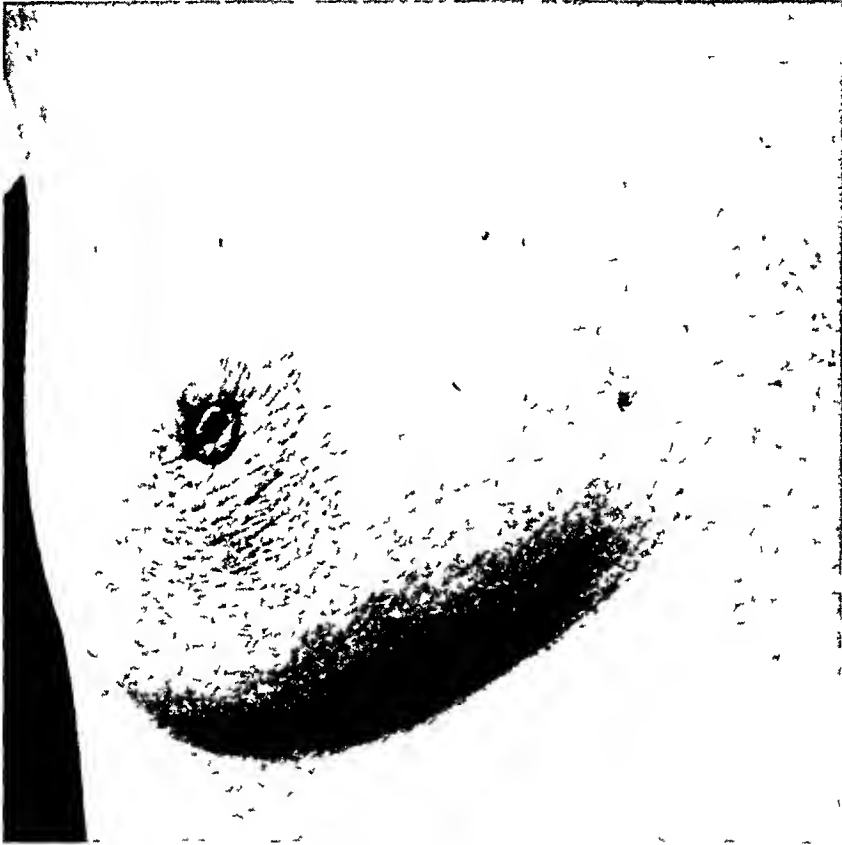


FIG 2—A small area of edema of the skin in the areolar region

When the area of edema is small, as in the case shown in Figure 2, it easily escapes detection unless carefully looked for. It usually begins in the skin within or just caudad to the areola, that is, in the more dependent part of the breast. This is regularly the site where edema first appears when the tumor is situated deep in the central part of the breast, but it may also be the earliest location of edema when the tumor is situated in the periphery of the breast. We have seen edema appear just below and medial to the areola when the carcinoma was a small one situated in the extreme upper outer limits of the breast.

This tendency for edema of the skin to develop in the areolar region is very likely due to the fact that the carcinoma of the breast tends to spread, in its late stages, in a retrograde direction along the main lymphatic pathways

accompanying the ducts converging at the nipple. Reaching the dermal lymphatics in the areolar region the carcinoma plugs them so completely that edema in the immediately adjacent dependent area of skin results.

There are, of course, other cases in which the edema first appears in the skin immediately over a carcinoma situated more peripherally in the breast. In such cases the skin is usually somewhat adherent to the underlying tumor, and it seems probable that the skin lymphatics have been obstructed by direct retrograde invasion from the surface of the growth outwards.

We have been much interested in the mechanism by which edema of the skin is produced, and we have made a special effort over a period of years



FIG. 3.—Carcinoma emboli in dilated lymphatics in the corium of edematous skin.

to study the skin histologically in these cases. In interpreting the findings the first requisite, of course, is an appreciation of the normal arrangement of the lymphatics in the skin. Since the classical studies of von Reichmann,¹¹ it has been known that there are no lymphatics in the epidermis itself. In the corium, however, there are two networks of them, a narrow-meshed superficial one which sends branches up around the papillae, and a wide-meshed deeper one made up of broader channels equipped with valves which communicate by means of vertical branches with the subdermal lymphatics. Our histologic studies of edematous skin have led us to the conclusion that the process begins with the appearance of embolic masses of carcinoma cells in the deep network of lymphatics in the corium. We assume that the mechanism by which extension takes place is at first *embolic* rather than one of *continuous permeation*, because we have often seen the picture illustrated in

Figure 3 Here, in edematous skin, the deeper lymphatics are dilated and contain unmistakable tumor emboli. As the edema progresses both the superficial and deep lymphatic vessels become solidly choked with tumor cells, and at this advanced stage of the process permeation is probably the predominant mechanism by which the disease extends.

Leitch, and all those who have written regarding inflammatory carcinoma since his time, have assumed that edema is due to continuous permeation of the skin lymphatics by the carcinoma. Leitch records studying a total of only seven cases in which there was edema, and all of these were apparently far advanced, so that he may not have had the opportunity of studying the histologic appearance of the early stage of edema. It is probable, also, that Leitch was influenced toward emphasis upon permeation as opposed to embolism as the method by which breast carcinoma spreads by his confrere Sampson Handley. For, in 1905, when Leitch was studying cases with edema, Sampson Handley was working in the same laboratory at Middlesex, completing his interesting investigations of the process of dissemination of breast carcinoma.

When edema involves a large area of skin over the breast, the dermal and subdermal lymphatics are extensively involved. This explains the clinical fact that patients with edema involving a considerable part of the skin over the breast are never cured by surgery. When tumor embolism and permeation have progressed to such an advanced stage it is only reasonable to find that the disease is beyond the limits of any local surgical attack, no matter how radical it may be. This, at least, has been our experience at the Presbyterian Hospital.

In order to determine as accurately as possible the significance of edema of the skin we classified the cases in which this phenomenon was present into two groups: (1) Those in which the extent of the edema was *limited to less than one-third of the skin over the breast*, and (2) those in which it *extended over a larger area*.

There were a total of 41 patients with *extensive* edema of the skin in whom radical mastectomy was performed. Twenty-seven, or 65.9 per cent, were known to have developed local recurrence within five years following operation. None remained cured at the end of five years. We have, therefore, placed this group of cases in our *categorically inoperable* class.

The results of radical mastectomy in the patients with *limited* edema are shown in Table XIV, from which the groups of cases classified by us as *categorically inoperable* have been excluded.

TABLE XIV

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THERE WAS LIMITED EDEMA OF THE SKIN OVER THE BREAST
(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence No	Per Cent	5-Year Clinical Cures No	Per Cent
Limited edema only	32	13	40.6%	4	12.5%
Limited edema with other signs of locally advanced disease	17	12	70.6%	0	
Total	49	25	51.0%	4	8.2%

These data indicate that edema of the skin, even when it is of very limited extent, is an extremely serious sign. In the group of cases in which this grave sign occurred alone the cure rate was but 12.5 per cent, and when it occurred in conjunction with other signs of locally advanced disease there were no cures.

When we state that edema is a grave sign we mean, of course, that it is a grave sign when it is produced by carcinoma. For edema of the skin over the breast develops, although infrequently, in a variety of other conditions. It is sometimes seen, for instance, when the axillary lymph nodes are extensively involved by tuberculosis. Breast abscess produces it. We have also seen it develop in association with a cyst around which there was a marked granulomatous proliferation. In these conditions the lymphatic blockage must be due to the inflammatory process. The diagnostician should take care not to jump to the conclusion that a patient has carcinoma just because she has edema, for in itself this sign is not diagnostic.

FIXATION OF THE TUMOR TO THE CHEST WALL

As carcinoma of the breast extends locally, the growth itself, as well as the breast in which it lies, tends to become fixed to the underlying pectoral fascia, and finally to the thoracic cage. It is important to define this fixation in terms of degree. All surgeons are familiar with the advanced degree of fixation in which the breast is more or less immovable upon the chest wall. But the early stage of the process often escapes the examiner's attention for it is brought out only by certain special maneuvers.

Early fixation can be demonstrated by having the patient sit erect, place her hands on her hips, and contract her pectoral muscles by pressing her hands against her sides first on one side and then on the other. The breasts, if they are not too heavy, are normally pulled upward slightly by this action. The upward motion is usually apparent only along the lateral aspect of the breast where the movement of the underlying pectoral muscle is greatest. There is usually no upward movement of the lower, dependent edge of the breast. But when carcinoma has produced abnormal fixation of the breast to the underlying pectorals the affected breast is pulled upwards more than its normal mate. This abnormal elevation may be apparent only along the lateral aspect of the breast, or in the region of the tumor. In cases with more advanced fixation the whole breast may be elevated by pectoral contraction. This is what we have chosen to designate as first-degree fixation. The breast and the tumor within it can still be moved passively with freedom over the chest wall.

Another maneuver to demonstrate abnormal fixation of the tumor to the chest wall is carried out with the patient lying supine, the hands placed on the hips. With the pectorals relaxed, the examiner first tests the movability of the tumor over the chest wall by gently moving it upwards and downwards in the direction of the long axis of the body. The patient is then asked to press her hands against her sides, contracting the pectorals,

and the movability of the tumor over the chest wall is again tested. When this maneuver shows that movability is decreased by contraction of the pectorals we assume that it is due to abnormal fixation to the underlying pectoral fascia, and designate it in our classification as second-degree fixation.

A more advanced degree of fixation, and one which we call third-degree fixation, is that in which the tumor is more or less solidly fixed to the underlying chest wall, even when the pectorals are relaxed.

In general, the surgeons who described the physical findings, in years gone by, in the series of cases we are here discussing did not distinguish the lesser degrees of fixation which we have mentioned. We have had to be content, therefore, with sorting out only the group of cases in which the tumor was solidly fixed to the chest wall. The results of treatment in this group, excluding the *categorically inoperable* cases, are shown in Table XV. These results indicate that a marked degree of fixation is a grave sign.

TABLE XV

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THE TUMOR WAS SOLIDLY FIXED TO THE CHEST WALL

(Categorically Inoperable Cases Excluded)

Clinical Group	No of Cases	5-Year Local Recurrence No	Per Cent	5-Year Clinical Cures No	Per Cent
Fixation <i>only</i>	18	7	38.9%	2	11.1%
Fixation <i>with</i> other signs of locally advanced disease	24	9	37.5%	2	8.3%
Total	42	16	38.1%	4	9.5%

There is a small group of cases of carcinoma developing in the inframammary fold which we have not included in Table XV, because they present a special problem as regards fixation. These tumors of the inframammary fold all appear to be fixed, even when they are small, because of the close attachment of the fascial planes to the body wall at this point. The breast, being an appendage of the skin, is enclosed between the superficial and deep layers of the superficial fascia. These layers fuse at the lower border of the breast and bind its edge to the fascial plane of the abdominal wall. In the present series there were five patients with fixed inframammary tumors in whom radical mastectomy was performed. One of them developed a local recurrence, but the other four, or 80 per cent of the group, were cured five years after operation. With this experience in mind, we do not attach any importance to fixation if the tumor is a small inframammary one.

SATELLITE TUMOR NODULES IN THE SKIN OVER THE BREAST

In the advanced stage of mammary carcinoma satellite tumor nodules frequently develop in the skin adjacent to the primary tumor. They are often better felt than seen, being detected by passing the flat of the hand gently over the skin surface. These nodules no doubt develop as the result of retrograde extension of the disease to the skin lymphatics.

The grave significance of the appearance of these satellite skin nodules

is known to most surgeons. In the present series of cases such nodules were noted in a total of 35 of the patients on their admission. Radical mastectomy was performed in only seven. Four of these developed local recurrence, and none was cured. This experience would indicate, therefore, that the presence of satellite nodules is a definite contraindication to radical mastectomy. We include this group of cases in our *categorically inoperable* class.

INTERCOSTAL OR PARASTERNAL NODULES

Secondary nodules of breast carcinoma sometimes appear along the intercostal spaces or in the parasternal region. Their origin must be from the external or the internal intercostal lymphatics, which course posteriorly and anteriorly, respectively, beneath the intercostal muscles. The nodules appear, presumably, when masses of tumor cells become lodged at some particular point along these comparatively large lymphatic channels, and grow to form a secondary tumor nodule that becomes apparent externally. At the sternal edge such nodules lie at the point where the lymphatic channels perforate the chest wall to reach the internal mammary chain of nodes.

It has been our experience that cases in which such secondary intercostal or parasternal nodules are present are beyond the scope of surgery. In the present series of cases radical operation was undertaken in only one such case, and cure was not obtained. We have, therefore, put these cases in our *categorically inoperable* class.

MASSIVELY ENLARGED AXILLARY NODES

Although the accuracy with which the size and consistency of axillary lymph nodes can be determined clinically depends to a considerable extent upon the obesity of the patient, we believe that a careful estimation of their actual size in terms of centimeters should always be attempted. Measurement of the *vertical* diameter of a mass of axillary nodes does not mean a great deal, for a chain of small- or medium-sized nodes fused together may extend a relatively long distance vertically. The estimation of the *transverse* diameter of the largest node or mass of nodes is more truly indicative of the extent of disease, and it is upon this measurement that our experience has taught us to rely.

In the series of cases which we are considering here the examiner usually failed to record actual clinical measurements of the nodes, being content to state that they were moderately or massively enlarged. Unfortunately, statements of this kind do not lend themselves to statistical analysis because massive enlargement means one thing to one examiner and something else to another. There were only 24 cases in our series treated by radical mastectomy in which the transverse diameter of the largest axillary node was recorded as being 2.5 cm. or more. These data, even though they are not large, are worthy of close attention.

In all but one of these patients histologic examination after operation confirmed the presence of metastases. This one patient presented certain unusual features. She was a woman, age 30, with a large, relatively circumscribed tumor occupying the upper central part of the breast. The tumor measured 8 x 10 cm but it was freely movable over the underlying chest wall and there was no edema of the overlying skin. Massively enlarged but movable lymph nodes were visible in the axillary, and in infraclavicular and supraclavicular regions on the tumor side. These nodes measured as much as 3 cm in diameter. When radical mastectomy was performed the surgeon was surprised to find that none of these greatly enlarged nodes contained metastases, and the woman remains well, ten years after operation. In retrospect, it can be said that the only clinical feature of this case that justifies classifying it as inoperable was the massive lymph node enlargement. If biopsy of the most prominent nodes had been done it would have shown them to be free of metastases, and the radical mastectomy would then have been in order. This experience leads us to recommend biopsy whenever massive enlargement of axillary nodes is the deciding factor in judging operability.

In the remaining 23 cases in the present series in which clinical measurement of the axillary nodes showed them to be 2.5 cm, or more, in transverse diameter radical mastectomy gave very poor results, particularly in the group of cases in which the factor of large nodes was combined with other signs of locally advanced disease. These data are shown in Table XVI, which does not include the cases classified by us as *categorically inoperable*.

TABLE XVI

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH THE AXILLARY LYMPH NODES MEASURED 2.5 CM, OR MORE, IN TRANSVERSE DIAMETER CLINICALLY AND CONTAINED METASTASES

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence No	5-Year Local Recurrence Per Cent	5-Year Clinical Cures No	5-Year Clinical Cures Per Cent
2.5 cm lymph nodes <i>only</i>	10	2	20.0%	2	20.0%
2.5 cm lymph nodes <i>with</i> other signs of locally advanced disease	13	8	61.5%	1	7.7%
Total	23	10	43.5%	3	13.0%

FIXATION OF AXILLARY LYMPH NODES

As involvement of the axillary lymph nodes by carcinoma progresses the disease breaks through the capsule of the nodes and invades the fat and connective tissue of the axilla. Finally, a stage is reached in which the involved nodes become fused together and fixed to the overlying skin and immobile upon the chest wall forming the inner wall of the axillary space. This condition is easy for the examiner to detect in thin patients, but presents more difficulty in obese ones. The fixation to the axillary skin may be apparent as a zone of skin dimpling, and thus forms a visible sign

CARCINOMA OF THE BREAST

TABLE XVII

RESULTS OF RADICAL MASTECTOMY CASES IN WHICH AXILLARY NODES WERE FIXED TO SKIN OR CHEST WALL

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No of Cases	5-Year Local Recurrence No	Per Cent	5-Year Clinical Cures No	Per Cent
Fixed axillary nodes only	7	1	14 3%	1	14 3%
Fixed axillary nodes, with other signs of locally advanced disease	14	7	50 0%	0	
Total	21	8	38 1%	1	4 8%

The significance of fixation of the nodes to the skin or the chest wall in cases in the present series treated by radical mastectomy is shown in Table XVII. The groups of cases classified by us as *categorically inoperable* have been omitted from this table. It will be seen that the results of operation in these cases with fixed axillary nodes were very poor. There were no cures at all in the group of cases in which this feature of fixed axillary nodes occurred in combination with other signs of locally advanced carcinoma.

EDEMA OF THE ARM

Edema of the arm is a sign that develops only when the axillary metastases of breast carcinoma have progressed to the stage in which they effectively block the lymphatic pathway through the axilla. The arm then begins to swell and often becomes painful. We have never known of a case in which this sign was present to be cured by radical mastectomy. In the present series operation was performed in three such cases and none was cured.

This experience has led us to place patients who present themselves with edema of the arm in our *categorically inoperable* group.

It might be added that the edema of the arm that develops *following radical mastectomy* is a very different process. There is often an inflammatory element in the causation of this kind of edema. It ordinarily has no special prognostic significance.

SUPRACLAVICULAR METASTASES

At the turn of the century, Halsted,¹² who devised the first truly radical mastectomy, had extended his operation to include dissection of the supraclavicular region. He omitted it only in the hopeless cases, in "duct cancers," and in the well-differentiated adenomatous types of tumor in which the axilla was not involved. By 1907, when he reported the three-year end-results in his series of 232 cases, he had performed supraclavicular dissection in 119 cases. In 44 of these 119 cases the supraclavicular nodes, as well as the axillary nodes, were proved to be involved. Three of these 44 patients were well three years after operation.

Despite Halsted's endorsement of supraclavicular dissection, the operation has lost favor, and is today generally abandoned even by most of Doctor Halsted's pupils. Whether this is because present-day surgeons are unwilling to perform an operation that yielded only a seven per cent cure rate even

in Doctor Halsted's hands, or whether their results with the operation have not been as fortunate as his, is difficult to say. It seems more likely that the latter is the best explanation. Eggers¹⁷ has recently reported his results with supraclavicular dissection in breast carcinoma. He performed the operation upon 14 patients in whom supraclavicular nodes were palpable. None of them survived beyond four years.

In our data from the Presbyterian Hospital the results of supraclavicular dissection in cases with clinically involved supraclavicular nodes were equally discouraging. In a total of 48 of the 986 patients for whom detailed records were available, enlarged supraclavicular nodes were discovered on admission,

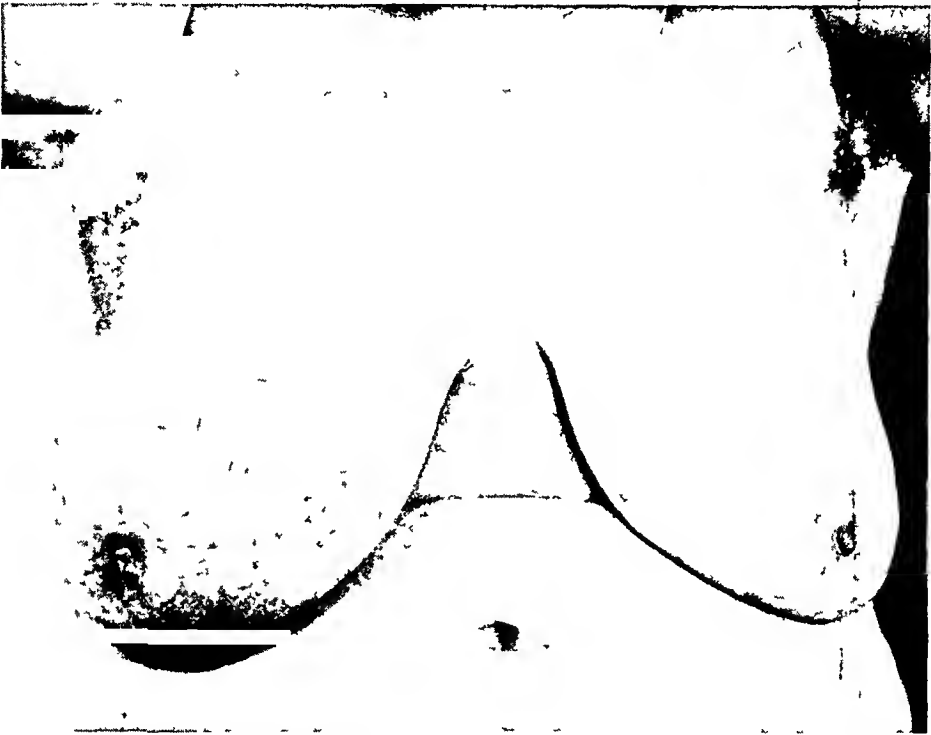


FIG. 4—The inflammatory type of breast carcinoma

that is in 4.9 per cent. Supraclavicular dissection was done in a total of 16 cases. In four of these, histologic examination showed the nodes were not involved. In the group of 12 remaining cases, in which the nodes did contain metastases, there were no five-year cures. Only four of these dissections were carried out at the time of the radical mastectomy. Three of the others were operated upon as a separate procedure shortly after radical mastectomy. In the remaining five cases the dissection was done at the time the supraclavicular nodes became palpable, from 10 to 48 months after radical mastectomy.

This experience has convinced us of the futility of supraclavicular dissection in patients in whom supraclavicular nodes are palpable. We have, therefore, classified these patients in our *categorically inoperable* group.

The use of supraclavicular dissection as a prophylactic procedure for

CARCINOMA OF THE BREAST

patients in whom there is no clinical evidence of supraclavicular metastases but who have proved axillary involvement, is not so easily dismissed. The dissection, if properly done, is practically without mortality when carried out as a separate procedure subsequent to radical mastectomy. Since radiation, in our experience, will not cure supraclavicular metastases, surgeons who are willing to undertake a great amount of operating to salvage only three or four patients out of every hundred, may one day take up supraclavicular dissection again for use in carefully selected cases. It is a poor resource, but it is the best that we have.

INFLAMMATORY CARCINOMA OF THE BREAST

In any discussion of operability the so-called *inflammatory* type of breast carcinoma merits special consideration. In recent years this acute and fatal form of the disease has been well described by American and German writers. Taylor and Meltzer included a comprehensive bibliography in their 1938 paper.

The accompanying photograph (Fig. 4) shows a typical example of this disease. The patient, Hosp. No. 383920, a woman, age 58, came to the hospital complaining of a tumor of the breast of six weeks' duration. The right breast was almost twice the size of the left one, and the skin over it was reddened, edematous, and warmer than the skin over the other breast. Although the entire breast was indurated, there was, in addition, a hard tumor, measuring about 12 cm. in diameter, in the center of the organ. The nipple was retracted. In the right axilla there was a mass of hard nodes measuring 3 cm. in diameter, transversely. A radical mastectomy was performed. As might be expected with this type of disease there was prompt local recurrence in the field of operation on the chest wall, and the patient died with liver metastases, eight months after operation and nine and one-half months after the onset of her disease.

In the series of cases which we are reporting here there was a total of 28 patients with the inflammatory type of carcinoma. In 20 of them radical mastectomy was performed. Half of these were known to have developed local recurrence, and all succumbed to their disease within a relatively short time after operation. Some of the data regarding this group of cases are presented in Table XVIII.

This experience has led us to regard these patients with the inflammatory type of breast carcinoma as being incurable by operation. We classify them as *categorically inoperable*, and advise palliative treatment with radiation.

DISTANT METASTASES

A final factor in deciding as to the operability of breast carcinoma is the question of the presence of distant metastases. Every surgeon, of course, searches for them, but their demonstration is not always easy even with the best of our modern diagnostic aids.

TABLE XVIII

RESULTS OF RADICAL MASTECTOMY IN THE INFLAMMATORY TYPE OF TREATED CARCINOMA

A—Number of cases of <i>inflammatory</i> type in which radical mastectomy was carried out	20
B—Age of patients—varied from 38 to 61 Mean Age	47 years
C—Duration of symptoms on admission—varied from 1 week to 2 years Mean duration	7 4 months
D—Symptoms	
1—Pain	10
2—Tenderness	4
3—Diffuse enlargement of the breast	15
4—Widespread redness of skin over breast	20
5—Increased warmth of skin	5
6—Extensive edema of skin	19
7—Tumor palpable within breast	13
8—Two tumors in breast	1
9—Diffuse induration of breast, without a discernible tumor	8
10—Elevated body temperature	3
E—Local recurrence in 10 or 50 per cent	
F—Five-year clinical cures in none	
G—Mean length of survival following operation	15 5 months

It is our personal practice to carry out the following routine in searching for distant metastases in every new patient

- 1 Inquire particularly about the recent development of headache, and pain in the back and legs
- 2 Inquire regarding recent cough or pain in the chest
- 3 Run the hand gently over the skin of the back and chest In this way small skin metastases which can not be seen can often be felt
- 4 Palpate the opposite axilla and the supraclavicular regions for distant lymph node metastases
- 5 Palpate the abdomen, with special attention to the liver
- 6 Roentgenograms of the chest and skeleton

Each one of these methods of inquiry has, at one time or another, enabled us to detect distant metastases, and prevented useless radical mastectomy Before the days of radiation therapy there was some excuse for carrying out radical mastectomy upon patients with distant metastases, but today, with the palliative resource of radiotherapy at hand, the surgeon is certainly not justified in operating

We have come to feel that the entire skeleton, with the exception of the forearms and hands, lower legs and feet, should be studied roentgenologically We have seen isolated metastases in the humerus, skull, shoulder girdle, and lower femur that would have been missed if these bones had not been included A skeletal study of this kind requires six 14- x 7-inch, and three 10- x 12-inch films, but we believe that this expense is well worth while

The great majority of these breast carcinoma metastases in bone are osteolytic in type In films of the lower spine and pelvis, gas bubbles in the bowel often produce areas of lesser density which must be distinguished from osteolytic metastases The experienced roentgenologist usually is able to do this at a glance, but stereoscopic films may be required in some cases

The differential diagnosis of osteolytic lesions in bone, occurring in a female in middle and later life, who has a breast tumor is not difficult

On the basis of relative frequency they will be found to be due to metastases from the breast tumor in the overwhelming majority of cases. Myeloma and hyperparathyroidism, which also cause destructive lesions in bone, are rare diseases. Accompanying blood chemistry changes will serve to distinguish them when the roentgenologic appearance is equivocal. In the skull, the changes due to osteoporosis circumscripta and to fully developed Paget's disease (see Kasabach and Gutman¹⁴) may cause confusion, but the finding of sclerotic, osteoblastic Paget lesions elsewhere in the skeleton will usually settle the problem. In fully developed Paget's disease the elevated blood phosphatase is, of course, diagnostic. In one of the patients in the present series the skull changes of Paget's disease were for a time mistaken for metastases.

These resources will enable the experienced roentgenologist to make a definite diagnosis of metastases in the great majority of women with breast carcinoma accompanied by bone lesions. In cases in which vague bone lesions defy exact diagnosis even after careful stereoscopic study, and in which there is no clinical evidence to tip the balance of opinion, it has been our custom to assume that they do not represent metastases and to proceed with operation. This practice has not, to our knowledge, led us into the error of undertaking radical mastectomy upon inoperable cases.

But even when roentgenologic studies are negative, the presumptive diagnosis of bone metastasis can be made from the history alone in certain cases. This is particularly true of metastases to the thoracic and lumbar spine. The pain that most of these unfortunate patients develop is rather characteristic. They often describe its earliest manifestation as "stiffness" of the back. After a few weeks this becomes definite pain, which develops after exercise such as walking or standing up for long periods of time. The pain becomes steadily worse, limiting the patient's activity greatly. When she sits quietly, or lies in bed, she is perfectly comfortable, but getting up from a chair or out of bed becomes torture. The pain is usually centered in the back, but may radiate down either leg. It is markedly accentuated by jolting, as when the patient misses a step and comes down hard on one foot, or when the vehicle in which she is riding strikes a sharp bump. We have repeatedly made a presumptive diagnosis of metastasis to the spine in patients with this kind of a story whose roentgenograms were negative, and have withheld radical mastectomy. Radiotherapy is begun at once, and if the pain is relieved after an appropriate interval the response provides confirmation of the diagnosis. Further roentgenologic studies at monthly intervals will eventually provide proof of the presence of metastases.

The interval between the onset of pain and the roentgenologic demonstration of bone metastases from breast carcinoma is sometimes remarkably long. Lenz and Fried¹⁵ reported a series of cases of this kind in one, 12 full months elapsed before the spinal metastases were identified roentgenographically. The explanation for this long delay is found in the studies made by Chasin¹⁶. He found that in vertebrae, defects of from 1 to 1.5 cm

diameter made by removing the spongiosa, could not be demonstrated by the usual anteroposterior roentgenogram. Even when practically the entire spongiosa was removed, leaving only the cortex and the superior and inferior plates of the vertebra intact, he was unable to demonstrate the defect by films taken anteroposteriorly. These findings were corroborated by Bohmig and Prévot¹⁷ who were unable to demonstrate artificial defects the size of a cherry in the vertebrae by means of roentgenograms. We must, therefore, assume that when spinal metastases of breast carcinoma finally become apparent roentgenographically, the disease has already destroyed a great part of the structure of the vertebrae.

In the series of cases of breast carcinoma which we are here reporting, distant metastases were demonstrated on admission to the hospital in a total of 85, that is, in 97 per cent. In seven of these 85 patients radical mastectomy was, nevertheless, carried out. The situation of the distant metastases in these seven patients is detailed in Table XIX.

TABLE XIX

SITUATION OF DISTANT METASTASES DEMONSTRATED PREOPERATIVELY IN SEVEN PATIENTS TREATED BY RADICAL MASTECTOMY

A—In lymph node of contralateral axilla as proved by biopsy	1
B—In ovary, as indicated by the presence of a large lower abdominal tumor	1
C—In the liver as indicated by liver enlargement	1
D—In the spine as indicated roentgenologically	4

The reason for operating is not apparent from the records of some of these cases. In others, the operator chose to ignore the evidence of the presence of metastases on the basis of the philosophy of "giving the patient her one chance of cure, remote though it might be." The fallacy of this kind of thinking, of course, is that the patient in truth has no chance whatever of cure when the evidence of metastasis is definite. None of the seven patients listed above was cured.

It is our own practice to classify patients in which there is presumptive evidence of the presence of distant metastases as *categorically inoperable*. We treat them exclusively with radiation.

A RULE FOR JUDGING OPERABILITY

When our data regarding the results of radical mastectomy in the different groups of cases with the various clinical features which we have detailed above are combined into Master Tables, a rule for operability can be derived from them. The first Master Table includes only the groups of cases in which there were virtually no five-year clinical cures—the groups which we have classified as *categorically inoperable*. These are combined in Table XX.

The groups of cases in Table XX are not mutually exclusive. They total 74 cases, with a local recurrence rate of 48.6 per cent, and no permanent cures. Faced with these facts it is impossible to escape the conclusion

CARCINOMA OF THE BREAST

TABLE XX

RESULTS OF RADICAL MASTECTOMY IN CATEGORICALLY INOPERABLE GROUPS OF CASES

Clinical Group	No of Cases	5-Year Local Recurrence No	Per Cent	5-Year Clinical Cures No	Per Cent
Carcinoma developing during pregnancy or lactation	20	6	30 0%	1 (Recurrence after 6 yrs)	
Extensive edema of skin over breast	41	27	65 9%	None	
Satellite nodules in skin over breast	7	4	57 1%	None	
Intercoastal or parasternal nodules	1	0		None	
Edema of the arm	3	2	66 7%	None	
Proved supraclavicular metastases	12	7	58 3%	None	
Inflammatory type of carcinoma	20	10	50 0%	None	
Distant metastases	7	1	14 3%	None	
Total	74	36	48 6%	1 (Recurrence after 6 yrs)	

that cases of this kind should not be operated upon. They are truly *categorically inoperable*.

There remain several clinical factors indicative of the local extent of the disease regarding which our data are not as conclusive, particularly when these factors are considered individually. These data are combined in Table XXI. The groups of cases are small, but it should be kept in mind that they include only the cases in which the particular clinical sign in question was the only grave sign present, moreover, the *categorically inoperable* cases have been excluded.

TABLE XXI

RESULTS OF RADICAL MASTECTOMY IN GROUPS OF CASES EACH FEATURED BY A SINGLE CLINICAL SIGN INDICATIVE OF THE LOCAL EXTENT OF THE DISEASE

(Categorically Inoperable Cases Excluded)

Clinical Signs	No of Cases	5-Year Local Recurrence No	Per Cent	5-Year Clinical Cures No	Per Cent
1—A single tumor 10 cm. or more, in diameter	12	2	16 7%	3	25 0%
2—Multiple tumors in one breast	9	3	33 3%	4	44 4%
3—Redness of the skin	23	6	26 1%	8	34 8%
4—Skin involvement	21	6	28 6%	6	28 6%
5—Ulceration	9	1	11 1%	2	22 2%
6—Edema of limited extent	32	13	40 6%	4	12 5%
7—Fixation of tumor to chest wall	18	7	38 9%	2	11 1%
8—Axillary lymph nodes 2.5 cm. or more in diameter proved to contain metastases	10	2	20 0%	2	20 0%
9—Fixed axillary nodes proved to contain metastases	7	1	14 3%	1	14 3%

From Table XXI it is apparent that the presence of any single one of these various clinical signs of the local extent of the breast carcinoma is not a sufficient contraindication to radical mastectomy. The cure rate is rather lower, however, in the last five groups of cases in Table XXI than in the first four groups. This fact led us to test out in our data the prognostic significance of the presence of combinations of the various individual clinical signs with one or more of these five relatively unfavorable clinical factors, namely, ulceration, edema of limited extent, fixation of the tumor to the chest wall, axillary lymph nodes 2.5 cm. or more in diameter, proved to contain metastases, and fixed axillary lymph nodes, proved to contain metastases. Table XXII shows the results of radical mastectomy in cases

with these combinations of clinical signs. Here again, the *categorically inoperable* cases have been excluded, as have been the cases listed in Table XXI in which the various clinical signs occurred singly.

TABLE XXII

RESULTS OF RADICAL MASTECTOMY IN GROUPS OF CASES EACH FEATURED BY A COMBINATION OF SIGNS INDICATIVE OF THE LOCAL EXTENT OF THE DISEASE

(*Categorically Inoperable Cases Excluded*)

Clinical Group	No. of Cases	5-Year Local Recurrence No	5-Year Local Recurrence Per Cent	5-Year Clinical Cures No	5-Year Clinical Cures Per Cent
1—10 cm tumor <i>with</i> 5, 6, 7, 8, or 9	7	2	28.6%	1	14.3%
2—Multiple tumors <i>with</i> 5, 6, 7, 8 or 9	3	1	33.3%	0	0%
3—Redness of skin <i>with</i> 5, 6, 7, 8 or 9	30	13	43.3%	6	26.4%
4—Skin involvement <i>with</i> 5, 6, 7, 8, or 9	44	11	25.0%	8	18.2%
5—Ulceration <i>with</i> 6, 7, 8 or 9	14	4	28.6%	1	7.1%
6—Edema of limited extent <i>with</i> 5, 7, 8 or 9	17	12	70.6%	0	0%
7—Fixation of tumor, <i>with</i> 5, 6, 8 or 9	24	9	37.5%	2	8.3%
8—2.5 cm axillary lymph nodes proved metastases <i>with</i> 5, 6, 7, or 9	13	8	61.5%	1	7.7%
9—Fixed axillary lymph nodes proved metastases <i>with</i> 5, 6, 7, or 8	14	7	50.0%	0	0%

These data regarding the significance of combinations of clinical signs are of little or no value in Groups 1 and 2, because the numbers of cases are too small. In Groups 3 and 4 the cure rate is certainly high enough to justify radical mastectomy. In the last five groups of cases in Table XXII, however, the cure rate is so low that we doubt that operation was worth while. These groups of cases are not mutually exclusive, but the total number of cases falling into Groups 5, 6, 7, 8 and 9 is 35. The disease recurred locally before the end of five years in 16, or 45.7 per cent of these, and only two patients or 5.7 per cent, were well five years after operation. Both of them later developed local recurrence and died.

From these correlations we have drawn up a rule for judging operability in breast carcinoma as follows: *Women of all age-groups, who are in good enough general condition to run the risk of major surgery, should be treated by radical mastectomy, except as follows:*

- 1 When the carcinoma is one which developed during pregnancy or lactation
- 2 When extensive edema of the skin over the breast is present
- 3 When satellite nodules are present in the skin over the breast
- 4 When intercostal or parasternal tumor nodules are present
- 5 When there is edema of the arm
- 6 When proved supraclavicular metastases are present
- 7 When the carcinoma is the inflammatory type
- 8 When distant metastases are demonstrated
- 9 When any two, or more, of the following signs of locally advanced carcinoma are present
 - (a) Ulceration of the skin
 - (b) Edema of the skin of limited extent (less than one-third of the skin over the breast involved)

CARCINOMA OF THE BREAST

- (c) Fixation of the tumor to the chest wall
- (d) Axillary lymph nodes measuring 2.5 cm. or more, in transverse diameter, and proved to contain metastases by biopsy
- (e) Fixation of axillary lymph nodes to the skin or the deep structures of the axilla, and proved to contain metastases by biopsy

If these criteria had actually been followed in judging operability in the series of 640 radical mastectomies which we have reported, a total of 109 of the patients would not have been operated upon. Yet the number of patients permanently cured would not have been decreased by a single one. These facts are shown in Table XXIII.

TABLE XXIII
HAAGENSEN-STOUT CRITERIA OF OPERABILITY
APPLIED TO PRESBYTERIAN HOSPITAL SERIES OF RADICAL MASTECTOMIES
(1915-1934)

Group	No of Cases	5-Year Local Recurrence		5-Year Clinical Cures		Permanent Cures
		No	Per Cent	No	Per Cent	
Cases in which radical mastectomy was actually performed (1915-1934)	640	161	25.2%	231	36.1%	Many still well
Cases which we now would classify as inoperable	109	53	47.7%	3	2.8%	None
Cases which we now would classify as operable	531	109	20.5%	228	42.9%	Many still well

In the group of 109 cases which we would now, according to our rule for operability, classify as inoperable, there were three that remained well at the end of five years after operation. All three, shortly thereafter, developed local recurrence, with distant metastases, and died. Summaries of these cases follow.

Case 1—Hosp. No. 64106. M. W., colored, age 38. The tumor developed while she was nursing her first baby. It was 2.5 cm. in diameter, and situated in the upper outer sector of the breast. No local signs of inoperability. Radical mastectomy, one axillary node found to be involved. She was well at the end of five years, but, at six years, local intercostal recurrence and pulmonary metastases developed. She died seven and one-half years after operation.

Case 2—Hosp. No. 281668. L. P., age 43. Large, 14 x 12 x 8 cm., tumor filling the breast and fixed to the chest wall. Hard axillary nodes, more than 2.5 cm. in transverse diameter. Radical mastectomy, all nodes found to be involved. Well at the end of five years, but, ten months later, local recurrence appeared on the chest and in the axilla. Cervical metastases subsequently appeared, and she died eight years after operation.

Case 3—Hosp. No. 302431. M. B., age 59. The tumor measured 5 x 4 cm. and was situated in the upper inner sector of the breast. It had ulcerated through the skin, and was solidly fixed to the chest wall. Radical mastectomy, two axillary nodes involved. Well at the end of five years, but local recurrence on the chest wall and pulmonary metastases at the end of seven years. Died seven and one-half years after operation.

While radical mastectomy in this group of cases which we today classify as inoperable may, in rare instances, relieve the patient of evidence of her disease for as long as five or six years, there is another aspect of the

therapeutic problem which must not be lost sight of. It is the fact that the carrying out of a radical mastectomy in cases in which the carcinoma can not be wholly removed locally actually *shortens* the patient's life in the majority of instances. From our knowledge of the problem of the surgical attack upon cancer in general we, of course, know that any attempt at radical dissection which cuts through cancer tissue is futile. The cancer cells are disseminated throughout the wound and there is the possibility of their entering the blood stream as cancer emboli. Ordinarily, operations of this kind are followed by prompt local recurrence and by the development of distant metastases. We have repeatedly seen widespread distant metastases appear within a few months after radical mastectomy performed upon patients in whom the disease was locally entirely inoperable, quite as if the operator had produced a shower of cancer emboli.

The data as to length of survival in our series of cases (Table XXIV) substantiate this objection to the performance of radical mastectomy in inoperable cases. We have used as a basis for our comparison the data collected by Lazarus-Barlow and Leeming,¹⁸ and by Daland,¹⁹ as to the mean survival of patients with untreated mammary carcinoma.

TABLE XXIV

MEAN TOTAL DURATION OF BREAST CARCINOMA—ONSET TO DEATH—IN VARIOUS GROUPS OF CASES

A—Daland's series of 100 untreated cases	40 5 months
B—Lazarus-Barlow's series of 243 untreated cases	38 4 months
C—118 Presbyterian Hospital cases (1915-1934 series) regarded as inoperable and denied surgery and radiation	42 3 months
D—31 Presbyterian Hospital cases (1915-1934 series) regarded as inoperable and treated by simple mastectomy	38 0 months
E—104 Presbyterian Hospital cases (1915-1934 series) regarded as operable and treated by radical mastectomy but now classified as inoperable according to Haagensen-Stout criteria	32 3 months

These data suggest that the performance of radical mastectomy in cases in which the disease is locally so far advanced that cure can not be obtained shortens the patient's expectation of life by about ten months. Simple mastectomy may also shorten life somewhat. In these days, when radiation is available almost everywhere, we feel that, in general, it is the preferable method of palliation in these incurable cases. When the local disease is not checked by radiation and threatens to become an objectionable fungating tumor, and primary closure of the wound through grossly uninvolved tissue is technically possible, simple mastectomy is sometimes useful. But, in general, the less surgery that is undertaken upon the patients with incurable disease the longer they will survive.

As we emphasized at the beginning of this paper, the decision as to incurability, or rather inoperability, of breast carcinoma is difficult. We have suggested a rule for deciding the question, but we do not regard it as a definitive solution. We hope that other surgeons will test the validity of our criteria of operability upon their own series of cases, and by the use of statistical methods such as we have employed add to the knowledge of the problem.

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AMPUTATION NEUROMA IN NERVES IMPLANTED IN BONE¹

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WAR, the greatest single agent responsible for amputation, invariably stimulates interest in and a study of the problem of painful amputation neuroma. The various hypotheses advanced to account for the pain which occurs in a small percentage of these neuromas include Inflammation and ascending neuritis, strangulation of the neuraxes in contracting scar, fixation of nerve ends in muscle, and repeated trauma.¹ Treatment has been signally unsatisfactory, hence attention has been directed toward prevention of the neuroma or at least a minimization of its size and vulnerability. That such efforts have not been entirely successful is shown by the legion of suggested approaches to the problem.

Probably the oldest preventive method, one still commonly recommended, consists of pulling down the nerve as far as it will conveniently stretch, cutting it with a sharp scalpel and allowing the proximal end to retract into the areolar tissue well above the end of the stump.^{2,3} Baidenheuer⁴ (1908) modified this method by turning the cut end of the nerve back and implanting it beneath the sheath of the same nerve higher up, forming a loop. Kruger⁵ (1916) merely crushed the nerve in forceps. Sicaid⁶ (1916) felt that sensory fibers only would be destroyed by 60 per cent alcohol and recommended its use. Chapple⁷ (1917) turned back an epineurial cuff several millimeters in width, cut off the neuraxes and pulled down the cuff, tying it below the cut ends. Moskowicz⁸ (1918) inserted the end of the nerve into muscle. Corner⁹ (1918) excised an inverted wedge to form a "swinging door flap," the edges of which were sutured together. Hedri¹⁰ (1920) used the cautery to seal the end of the nerve and prevent the irritating effect of secretions from the wound. Hubei and Lewis¹¹ (1920) tied off the nerve and injected about one cubic centimeter of absolute alcohol from one to three centimeters above the site of the ligature. Stookey (1922) recommended a combination of Corner's swinging door flap and the injection of absolute alcohol. Lawen¹² (1925) used refrigeration. Foerster¹³ (1927) injected 5 per cent formalin into the central stump. Beswerschenko¹⁴ (1929) recommended Federoff's method of phenolization of the end of the nerve and the injection of liquid phenol into the stump above the cut end. Lexer¹⁵ (1931) tried electrocoagulation.

In reviewing this array of therapeutic proposals, it seemed noteworthy that the procedure of inserting the end of the cut nerve into the bone, invariably adjacent in amputations, had apparently not been tried by any of these

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authors Lewis¹¹ saw one instance of a divided nerve in which the ends had been driven into the bone—no neuroma was formed, and he believed that the surrounding bone prevented the formation of a bulb. Other relevant comment was not found in the literature. Craig and Walker¹⁶ (1942) observed a situa-

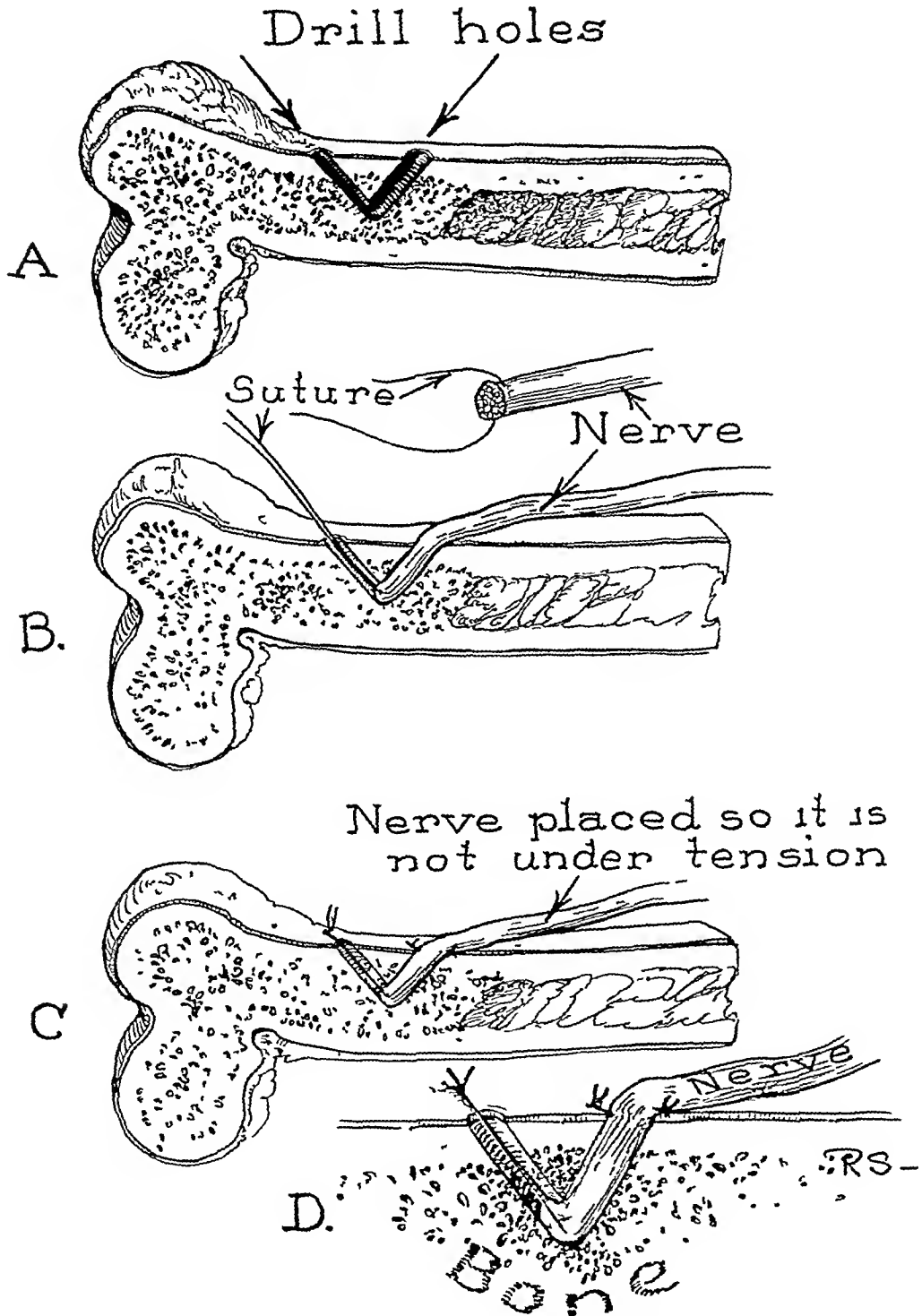


FIG 1—Technic for implantation of nerve into bone

tion similar to that noted by Lewis, in the arm of a patient wounded in the current war.

With these points in mind an experimental approach to the problem was begun in April 1942. It was decided to insert the ulnar nerve into a hole in

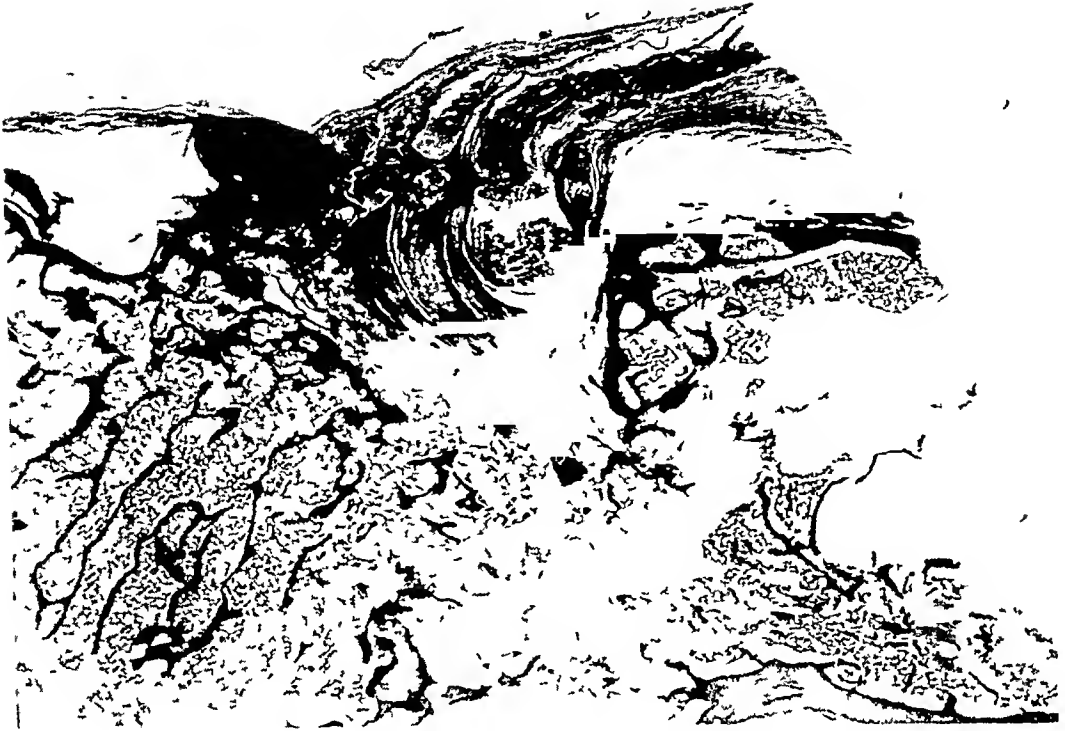


FIG 2—Photomicrograph of intra osseous amputation neuroma after 133 days (x6)



FIG 3—Photomicrograph of intra osseous amputation neuroma after 299 days (x6)

the distal portion of the humerus in dogs, and to observe the resulting amputation neuroma after the elapse of approximately 250 to 300 days—a figure chosen arbitrarily

Six large dogs were used. In each, the right ulnar nerve was exposed just over the distal end of the humerus. A hole large enough to contain the nerve was drilled into the cancellous bone above the joint and the nerve was cut and inserted into the opening, being held in place by fine cotton sutures placed between the periosteum and the perineurium. Fearing that the nerve might pull out—a fear substantiated later in two cases—a minor change was made in the last two experiments. A second, smaller hole was drilled into the bone below the first at an angle such that the two connected at the bottom of the



Fig. 4—Photomicrograph of amputation neuroma 318 days after operation. The nerve had pulled out of its intra osseous position ($\times 6$)

cavity of the larger hole. A suture was then passed through the perineurium and threaded through the two holes in the bone so that, by pulling on the suture, the cut end of the nerve was drawn into the depth of the opening and could be held there by attaching this suture snugly to the periosteum about the smaller hole. As in the earlier animals, stay-sutures between the periosteum of the larger hole and the adjacent perineurium were also used (Fig. 1)

The first dog on which this last technic was used was killed after only 133 days. Sections parallel with the long axis of the bone showed the neuroma to be small and completely beneath the cortex of the bone (Fig. 2)

The remaining animals were killed in from 262 to 318 days. The other dog upon which the modified technic was used had a small neuroma, completely subcortical, after 299 days (Fig 3). Two dogs in which the single-hole technic was used had only small neuromas, though somewhat larger than the one just mentioned. In one of these, after 276 days, the neuroma had burrowed deep into the bony tissue. Apparently a deeper cavity had been made in this instance. In a dog kept for 262 days, a cyst had replaced the distal one-third of the neuroma.

The two dogs in which the ulnar nerve had pulled out served as admirable controls. These were the first to be operated upon and their time of survival was slightly longer—318 and 314 days. In these two instances the neuromas were from two to four times the size of the buried neuromas (Fig 4).

During the course of this study the method was employed by Dr K O Haldeman and Dr Helen Hagey, of the Department of Orthopedics, in a case in which amputation was performed through the humerus because of a distally located malignant tumor. After five months there was no demonstrable neuroma in any of the nerves. The method has been used since in amputations carried out on the University of California Surgical Service at the San Francisco Hospital, thus far with no reported unsatisfactory results.

At present, studies are being made of the implantation of nerves into the fatty marrow and of combining the implantation of the nerve into bone with the injection of sclerosing agents to reduce further in size the ends of the cut nerves.

Statements concerning the value of implantation of the cut end of a nerve into bone for the prevention of painful amputation neuroma cannot be made at the present time. It can be concluded, however, that the method described is practicable, that the resulting neuroma will be small and that it will be protected from traumatic and toxic influences. On this basis further use of the method seems to be indicated.

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INTRAVENOUS GELATIN*

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THE USE OF GELATIN as a colloid for intravenous injection in the treatment of shock in man was first advocated by Hogan in 1915, who reported beneficial effects in six patients. Each received a single injection of 500 to 750 cc of what appeared to be approximately an 11 per cent solution in saline. Subsequently there was little interest in its use judging from the paucity of reports in the literature. However, Amberson states that Hogan's report was the first attempt to use a colloid clinically for infusion work and deserves recognition on that account since it stimulated Hurwitz (1917) and others to experiment with gum acacia. In 1937, Amberson, in a review of the question of blood substitutes stated "The use of the latter (gelatin) can no longer be recommended," inferring the superiority of gum acacia.

Because of the recent great interest in blood substitutes and also parenteral nitrogenous nutrition, the question of intravenous gelatin was again studied. The immediate purpose of the investigation was to determine whether or not gelatin injected intravenously may be well tolerated by man, especially if repeated injections are made, and also to determine if gelatin remains inert in the organism or can be metabolized. Studies on the possible nutritive value of intravenous gelatin in man have not been previously recorded.

The gelatin (pig skin in origin) employed was designated as "Sample 9," and was received from the manufacturer as a light brown powder. This was dissolved in distilled water to afford a 10 per cent solution and heated for 36 hours at 95° C (water bath). During heating the p_H of the solution was 4.5 and upon cooling the p_H was adjusted to 7.5-7.6 with NaOH, following filtration. Autoclaving, at 115° C and 15 pounds pressure was then carried out for 15 minutes for sterilization. After this step a precipitate formed and was removed by filtration. A second autoclaving was carried out and if the solution remained clear it was used for injections. If a precipitate formed again, this was removed by filtration and the solution autoclaved again. The initial prolonged heating reduced the viscosity of the solutions and lowered the gelling point. Heating also results in the breaking up of large gelatin molecules into molecules of smaller size. Evidence of this was afforded by the observations that the ammonia N/ was

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INTRAVENOUS GELATIN

0.8 per cent of total N/ in the gelatin before the 36-hour heating period and at the end of this period it was 1.4 per cent of the total N. Amino-N/ rose from 1.5 per cent of total N/ to 5 per cent of total N/ after heating

ANIMAL EXPERIMENTS

Preliminary observations as to the possible nutritive value of intravenous gelatin were made upon dogs maintained on a low protein diet ("Weech diet"—1.3 Gm N per 1200 caloric equivalent). After an initial period of observation, during which urinary nitrogen excretion and nitrogen intake were recorded (nitrogen balance studies), daily injections of 150 to 250 cc of 10 per cent gelatin solution were carried out for several days, this was followed by a period of observation without gelatin injections. The data are summarized in Table I.

TABLE I

NITROGEN BALANCE STUDIES IN DOGS RECEIVING LOW PROTEIN DIET AND GELATIN INTRAVENOUSLY

	Period	Days	Av Daily N per os Gm	Av Daily N Intrav Gelatin Gm	Av Daily N Loss Gm	Av Daily Urea N Excretion Gm	Daily Nitrogen Balance Gm
Dog 450	I	3	95	0	1.31	1.02	— .36
Wt 10 Kg	II	11	1.30	3.80	3.83	1.29	+1.27
	III	14	1.30	0	1.10	.47	+ .2
Dog 463	I	4	1.3	0	1.24	.71	+ .06
Wt 8.3 Kg	II	12	.83	3.05	2.00	.75	+1.86
	III	15	.87	0	.46	.25	+ .41
Dog 447	I	2	1.0	0	1.21	.90	— .21
Wt 7.4 Kg	II	10	.61	2.60	2.60	1.05	+ .61
	III	9	1.03	0	.80	.15	+ .23
Dog 449	I	3	.82	0	.875	.52	— .06
Wt 6.5 Kg	II	7	1.05	2.67	2.76	.75	+ .6
	III	3	0	0	2.67	.82	—2.67

In Dogs 450, 463 and 447 injections of gelatin permitted of positive nitrogen balance. This, or a nitrogen equilibrium, was maintained after cessation of gelatin injections, suggesting that all injected gelatin / was not immediately excreted during the injection periods. It is also to be noted that urea excretion was elevated slightly during the period of gelatin injections, and this, in the presence of a positive nitrogen balance and increased nitrogen intake (the increase being due mainly to gelatin), suggests that at least some of the gelatin was catabolized. Dog 449 refused to eat after the seven-day period of gelatin injections. The elevated total nitrogen excretion persisted after cessation of injections resulting in marked negative nitrogen balance, the nitrogen loss being in excess of the net nitrogen gain during the preceding period. Similar observations were noted in two other dogs. These findings are somewhat analogous to the observations of Elman that while nitrogen is injected as plasma in dogs, a positive nitrogen balance may obtain but that during the period subsequent to cessation of injections a negative nitrogen balance obtained which was approximately equivalent to the net nitrogen gain during the periods of plasma infusions. The cause for the above differences may be associated with several factors that depend

upon the general state of the animal. If the dogs refused to eat following the gelatin injections, the marked negative nitrogen balance obtained. When they did consume by mouth approximately what they did prior to the periods of gelatin injections, the net nitrogen gain resulting from these injections was maintained. Possibly the ingestion of amino-acids by mouth with the food protein—essential amino-acids that were not present in the gelatin (which is an incomplete protein)—is of major importance in facilitating the metabolism of gelatin injected by vein. Studies on the variations of plasma proteins in depleted dogs receiving gelatin were also carried out but will not be reported here since methods for differentiation of circulating injected gelatin and blood plasma proteins have not as yet proved satisfactory in the writers' experience.

OBSERVATIONS IN MAN

Three intravenous injections of several cubic centimeters of the 10 per cent gelatin solution in patients provoked no reactions. Larger amounts were injected in a number of patients and no reactions observed except in one patient who also exhibited chills and a moderate rise in temperature following injection of pooled human plasma. Patients presenting carcinomatosis were then placed on nitrogen balance regimen and gelatin (150 to 250 cc of 10 per cent aqueous solution) injected for three to twelve days consecutively. No reactions were observed. In some instances a second series of injections was made ten to fourteen days after cessation of the first series and no hypersensitivity was noted. In general, the injections appeared to be as well tolerated as saline infusions. The nitrogen balance studies in six patients are summarized in Table II.

TABLE II
NITROGEN BALANCE STUDIES IN HUMAN PATIENTS RECEIVING GELATIN INTRAVENOUSLY

Patient	Period	Days	Av. Daily N Intake by Mouth Gm	Av. Daily N Injected as Gelatin Gm	Av. Daily Total N Excretion Gm	Av. Daily Urea N Excretion Gm	Av. Daily N Balance Gm
I G F ♂	I	2	13.52	0	5.68	4.11	
52 years	II	4	12.00	3.00	7.38	4.16	
(carcinomatosis)	III	7	11.74	0	6.76	5.17	
II C J ♂	I	5	16.64	0	8.43	5.4	
34 years	II	5	15.00	3.00	12.00	7.58	
(small bowel fistula)	III	3	13.00	0	9.00	6.85	
III H H ♀	I	4	7.90	0	6.44	4.26	+1.46
42 years	II	4	6.90	2.27	9.00	4.92	+1.17
(carcinomatosis)	III	8	6.76	0	6.54	5.22	+1.22
IV B F ♀	I	7	6.00	0	4.57	3.44	+1.45
54 years	II	10	3.60	2.2	4.60	3.87	+1.20
(carcinomatosis)	III	10	4.40	0	3.14	2.10	+1.26
V C J ♂	I	2	0	0	3.76	1.42	-3.76
34 years	II	3	0	4.34	7.72	2.73	-2.38
	III	4	0	0	5.55	2.65	-5.55
VI R L ♀	I	4	7.76	0	4.84	3.84	+2.92
32 years	II	3	7.41	3.10	6.16	2.75	+4.35
(carcinomatosis)	III	3	7.57	0	4.18	2.27	+3.39

In Patient I, who had had a total gastrectomy for carcinoma and was in an advanced stage of carcinomatosis, a substantial portion of the stools was lost, hence no attempt is made to record nitrogen balance. He was given a very high caloric high protein diet. The total urinary excretion of nitrogen increased during the period of gelatin injections. The urea nitrogen increased during the subsequent period of observation, while the total urinary nitrogen decreased. This would suggest retention of some gelatin for a period, with delayed catabolism of it.

Patient II presented a small bowel fistula and, hence, while on a high caloric high protein diet it was not practicable to collect and analyze stools. Total urinary nitrogen increased during the injection period. The urea N was elevated during this period and decreased during the period subsequent to injection although it remained substantially above the level of the first period even though intake of N by mouth was greater during the first period. Here, again, it is suggested that at least some of the gelatin was catabolized.

Patient III was in positive nitrogen balance prior to injection of gelatin. When the latter was carried out in addition to the nitrogen ingested by mouth, the total nitrogen intake being increased, nitrogen equilibrium obtained. After gelatin injections ceased but nitrogen by mouth remained about the same, nitrogen equilibrium was maintained although urea nitrogen excretion increased. Again, the evidence suggests catabolism of gelatin.

In Patient IV total nitrogen intake during Period II was equal to the nitrogen intake during Period I, although during Period II 38 per cent of the nitrogen intake was in the form of intravenous gelatin. Urea N excretion during the second period was elevated, positive nitrogen balance was also practically as great as during the first period. During Period III the positive nitrogen balance was maintained. Total N and urea N excretion fell, due to decreased total N intake. In this patient intravenous gelatin appears to have effectively substituted for some of the protein taken by mouth.

In Patient V no food was taken by mouth, and he received nitrogen only as intravenous gelatin. The net nitrogen loss was less during the injection period than before or after injections. The urea N excretion increased during the injection period and remained elevated during Period III after injections ceased. This increased urea N excretion during and after the injection period could hardly be accounted for on any other basis than catabolism of the injected gelatin.

Patient VI ingested by mouth a constant amount of protein during the three observation periods. When additional nitrogen in the form of intravenous gelatin was given, the total N excretion increased but not sufficiently to prevent increased positive nitrogen balance which increase persisted during the period following gelatin injections. The urea N excretion did not increase in Periods II and III, thus this patient provides an exception, in this respect, compared with those cited above. The in-

crease in positive nitrogen balance suggests that there was increased storage of N under the conditions of the experiment (In some dogs, not reported above, gelatin injections were also followed by periods of reduced urea N excretion, the explanation for these exceptional instances is not clear)

DISCUSSION —Gelatin is an incomplete protein, in that all essential amino-acids are not present. Therefore, alone, it cannot be expected to afford an efficient source of nitrogenous substances for protein synthesis. That gelatin is well tolerated when injected intravenously has again been demonstrated in man. This tolerance extends to repeated daily injections and a hypersensitivity does not develop. Evidence was observed to suggest that gelatin injected intravenously is not inert but that at least part of it is catabolized, since increased urea N excretion usually obtains when such injections are made. In the absence of elevated temperature and where ingestion of N as food protein is more or less constant, the increased urea N excretion which signifies increased protein catabolism could hardly have resulted from other sources than the injected gelatin. One alternate possibility is that gelatin stimulates catabolism of body protein stores and thus the increased urea N was not from gelatin itself. This explanation, however, would presuppose substitution of gelatin molecules for body protein molecules, since positive nitrogen balances obtained in the above experiments. Such an explanation would seem to be farfetched. A portion of the gelatin injected intravenously is excreted in the urine unchanged, and possibly some of the molecules may be retained, for a period at least, unchanged within the body, thus complete catabolism of a given quantity of gelatin injected intravenously does not obtain (Brunschwig, Scott Corbin and Moe)

It would appear, therefore, that nitrogen may be introduced intravenously with comparative safety into the organism, in the form of incomplete protein molecules—gelatin. Since the latter does not include all essential amino-acids gelatin alone is an inadequate source of nitrogen for nutritional purposes. The fact that it is a colloid, however, and is not inert but is at least partially catabolized by the organism suggests possibilities for further investigation of gelatin as a parenteral nitrogenous nutriment when the missing essential amino-acids may be added either parenterally or *per os*.

In conclusion mention may be made of the fact that gelatins vary widely in character depending upon the source and methods of manufacture. In a study such as reported above, the results cannot be applied *a priori* to all types of gelatin.

CONCLUSIONS

- 1 Some types of gelatin, injected intravenously in human patients, are well tolerated
- 2 Evidence is presented to suggest that some of the gelatin injected

intravenously is catabolized, in that there is an increase in urea N excretion during and/or following the injections in man

3 Intravenous injection of gelatin appears to constitute a method for administration of nitrogen that might be utilized for nutrition. Gelatin as an intravenous nitrogenous nutriment has the same disadvantages as gelatin *per os*, in that it is an incomplete protein as it does not include all essential amino-acids. It cannot, therefore, be anticipated that nitrogen requirements for nutrition may be met by intravenous gelatin as the sole source of nitrogen.

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THE SURGICAL TREATMENT OF MALIGNANT LYMPHOMA

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IT HAS BECOME INCREASINGLY EVIDENT that the gloomy outlook held for individuals suffering from malignant lymphoma must be modified in certain instances¹. In an earlier study^{1, 2} it was shown that attention to cytologic detail permitted a division of these cases into subgroups on the basis of which a considerable range of prognosis could be given. Within each of these subgroups a majority of the patients followed a predictable course. A certain number, however, outlived their fellows to a remarkable degree, in fact some appeared to have been freed of their disease. Among these were many who instead of receiving the usual roentgenotherapy had at the outset been subjected to radical operative procedures.

The present study is concerned with forty-eight such cases which have in common the fact that all grossly perceptible evidence of lymphoma was surgically eradicated at an early operation.

In accordance with the nomenclature utilized in previous studies^{1, 2} these cases have been classified into the following seven groups: Stem cell lymphoma, clasmatocytic lymphoma, lymphoblastic lymphoma, lymphocytic lymphoma, Hodgkin's lymphoma, Hodgkin's sarcoma, and follicular lymphoma. For the details of this classification the reader is referred to the articles cited above. For purposes of comparison with other systems of nomenclature it may be said that the stem cell and clasmatocytic groups probably together comprise the bulk of the tumors commonly included under the term reticulum cell sarcoma^{3, 4}. The lymphoblastic and lymphocytic types correspond to what has usually been called lymphosarcoma^{5, 6}. Follicular lymphoma has been named giant follicle lymphoblastoma⁷ and even giant lymph follicle hyperplasia⁸. The expression cellular Hodgkin's disease is roughly equivalent to our Hodgkin's sarcoma and many authors undoubtedly include these cases as variants of reticulum cell sarcoma^{3, 9}.

That great differences in prognosis are associated with variations in cytologic type, may be seen by a glance at Table I (reproduced from the earlier study¹).

The cases in the present series include, as may be seen in Table II, representatives of each of the subgroups with a predominance (27 out of 48) of the four malignant types. In spite of this apparently unfavorable distribution the median survival period for the group as a whole was 4.5 years, more than twice that of the large control series the majority of the cases of which were treated by roentgenotherapy alone.

The number of cases in certain of the subgroups is undoubtedly too small

MALIGNANT LYMPHOMA

TABLE I

DURATION OF MALIGNANT LYMPHOMA (YEARS)

(618 Cases Miscellaneously Treated)¹

Type	Average	Median
Lymphoblastic lymphoma	1.4	0.6
Hodgkin's sarcoma	1.8	0.9
Stem cell lymphoma	1.7	1.1
Clasmatocytic lymphoma	2.1	1.1
Lymphocytic lymphoma	3.3	2.4
Hodgkin's lymphoma	4.2	3.2
Follicular lymphoma	5.6	5.0

TABLE II

EFFECT ON SURVIVAL

(Radical Surgery versus Roentgenotherapy)

Type	Number of Cases	Range of Survival (years)	Median of Surgical Group (years)	Median of X-Ray Group (years)
Lymphoblastic lymphoma	5	0.2-2.5	0.2	0.6
Hodgkin's sarcoma	2	0.0-0.2	0.2	0.9
Stem cell lymphoma	9	0.0-15.3	5.0	1.1
Clasmatocytic lymphoma	11	0.2-16.5	4.9	1.1
Lymphocytic lymphoma	9	0.0-10.0	5.5	2.4
Hodgkin's lymphoma	9	0.0-19.0	5.4	3.2
Follicular lymphoma	3	4.5-8.5	7.5	5.0

to warrant conclusions. In the stem cell and clasmatocytic groups (20 cases), however, the median survival periods are nearly five times as long as in the control series and in the lymphocytic and Hodgkin's lymphomas (18 cases) nearly twice as long. The figures are sufficiently arresting to justify attention and analysis.

Admittedly, these cases must be considered highly selected from a surgical viewpoint, since there have been excluded those in which the operator was not satisfied that he had removed all visible and palpable neoplastic tissue. It is believed, however, that the cases chosen may be considered as fairly representative of the lymphomatous group of diseases. All seven types were present. The age and sex incidences of the surgical series are identical with those of the larger series previously reported. The average age at onset was 41.1 years, and the proportion of males to females was 2:1.

There was wide variation in the duration of symptoms preceding operation, ranging from a few days (recorded as 0.1 years) to five years. The average preoperative duration of symptoms was 1.0 years, the mean 0.5 years. In the larger series of miscellaneously treated cases the average pre-treatment period was 1.3 years. It does not appear, therefore, that the patients included in the present study received therapeutic attention significantly earlier than the general run of individuals with the same disease. Moreover, it is apparent from Table III that the preoperative duration of symptoms bore no relationship to postoperative survival.

None of the patients received preoperative roentgenotherapy, which is not surprising since the histologic nature of the lesion was unsuspected in

TABLE III
CASES TREATED WITH RADICAL SURGERY

Case	Type	Location	Preop Duration (Years)	Postop Duration (Years)	Postop Recurrence (Years)	Postop Radiation	Status
1	Lymphoblastic	Cecum	0 5	0 2	?	Prophylactic	Dead
2	Lymphoblastic	Jejunum	1 0	1 5	0 8	Prophylactic	Dead
3	Lymphoblastic	Rectum	0 1	0 2	0	Prophylactic	Dead
4	Lymphoblastic	Stomach	3 0	0 2	0 2	0	Dead
5	Lymphoblastic	Sigmoid	1 0	2 5	1 0	Recurrence	Dead
6	Hodgkin s sarc	Jejunum	0 5			0	Lost
7	Hodgkin s sarc	Ax L N	3 5	0 2	0 2	Recurrence	Dead
8	Stem cell	Cerv L N	0 5	11 5	1 5	Recurrence	Dead
9	Stem cell	Thigh	0 7	15 3	7 0	Prophylactic	Dead
10	Stem cell	Cord (epidural)	0 1	2 6	2 0	Prophylactic	Lost
11	Stem cell	Skin (arm)	0 5	10 0	0	Prophylactic	Alive
12	Stem cell	Stomach	3 5	0	0	0	Dead
13	Stem cell	Cerv L N	0 5	9 0	0 2	Recurrence	Alive
14	Stem cell	Stomach	1 5	5 0	5 0	0	Dead
15	Stem cell	Cecum	1 0	0 3	0 3	Prophylactic	Dead
16	Stem cell	Stomach	0 2	0 5	0 2	Recurrence	Dead
17	Clasmatocytic	Appendix	0 1	0 2	0 2	Recurrence	Dead
18	Clasmatocytic	Stomach	0 1	0 2	0	0	Dead
19	Clasmatocytic	Jejunum	0 1	0 2	?	Prophylactic	Dead
20	Clasmatocytic	Humerus	0 9	16 5	7 0	Recurrence	Alive
21	Clasmatocytic	Stomach	0 8	6 2	0	Prophylactic	Alive
22	Clasmatocytic	Stomach	0 6	4 4	3 0	0	Dead
23	Clasmatocytic	Tibia	2 0	7 0	0	0	Alive
24	Clasmatocytic	Femur	0 2	6 1	0	0	Alive
25	Clasmatocytic	Stomach	1 0	6 0	0	0	Alive
26	Clasmatocytic	Cerv L N	0 5	5 0	5 0	Prophylactic	Alive
27	Clasmatocytic	Maxill antrum	0 1	3 0	0	Prophylactic	Alive
28	Lymphocytic	Cerv L N	0 3	1 6	0 1	0	Dead
29	Lymphocytic	Ileum	0 2		?	0	Lost
30	Lymphocytic	Eyelid	?	8 0	0	0	Lost
31	Lymphocytic	Cerv L N	0 3	3 5	3 5	Recurrence	Lost
32	Lymphocytic	Stomach	0 1	7 0	0	Prophylactic	Alive
33	Lymphocytic	Skin -back	0 1	10 0	0	0	Alive
34	Lymphocytic	Femur	2 0	8 0	2 0	0	Alive
35	Lymphocytic	Parotid	5 0	6 0	3 0	Prophylactic	Alive
36	Lymphocytic	Parotid	0 2	3 5	0	Prophylactic	Alive
37	Hodgkin s	Ing L N	0 1	19 0	0	Prophylactic	Alive
38	Hodgkin s	Cerv L N	0 1	5 4	?	Prophylactic	Dead
39	Hodgkin s	Submaxill	2 0	3 0	0	0	Dead
40	Hodgkin s	Cerv L N	4 0	15 0	0 2	Recurrence	Alive
41	Hodgkin s	Colon	0 6	0	0	0	Dead
42	Hodgkin s	Ax L N	1 0	5 5	0	Prophylactic	Alive (Tbc)
43	Hodgkin s	Cerv L N	0 9	0 6	0 3	Prophylactic	Dead
44	Hodgkin s	Cerv L N	4 0	10 0	6 0	Recurrence	Dead
45	Hodgkin s	Cerv L N	0 8	2 0	2 0	Prophylactic	Lost
46	Follicular	Ing L N	2 0	4 5	0	0	Dead
47	Follicular	Ing L N	0 5	8 5	0	Prophylactic	Alive
48	Follicular	Cerv L N	1 0	7 5	0	Prophylactic	Alive

almost all instances Had the character of the process been known, it is probable that the dictates of custom would have precluded operation in the majority of the cases herein reported Postoperative prophylactic irradiation was administered to 21 patients in amounts varying from 600 r to 1800 r The results were inconclusive, and it is not possible to comment concerning the efficacy of the procedure Thirteen other patients received irradiation at a later time for recurrence of the original tumor The response in these individuals was satisfactory in eight instances

Six of the 48 patients were considered lost, although three remained under observation after operation for 26 years, 35 years and 8 years, respectively. Twenty-three cases were known to be dead but among these were several dead of causes unrelated to lymphoma. Nineteen patients were alive, and only one of these had shown evidence of lymph node disease at the last examination. All of the others had been free of symptoms or objective signs for three or more years.

Recurrence, either locally or elsewhere, was observed in 23 patients. The recurrence had appeared an average of 2.2 years after operation although in eight patients there had been an interval of three to seven years. Among the 23 patients who died there were 13 with recognizable lymphomatous lesions at the time of death, four in whom the cause of death was unknown and six with no evidence of lymphoma. The latter included five cases dying shortly after operation the deaths being presumably surgical in nature. Obviously, insufficient time had elapsed in these to permit the development of recurrence.

Six of the dead cases were necropsied. In four (0.2, 0.25, 2.5 and 10 years after operation) extensive lymphomatous infiltration was found. One case dead of postoperative intestinal obstruction and another who died of prostatism and peritonitis 4.5 years after operation showed no persistent residua of neoplastic disease.

Exclusive of the two cases who disappeared immediately after discharge from the hospital, the average postoperative survival period for all cases was 5.2 years and the overall total duration from the date of onset was 6.9 years. These figures are, respectively, two times and almost three times the levels of similar figures obtained from identical cases treated by other means.

TABLE IV
"CURED" CASES OF MALIGNANT LYMPHOMA

Case	Type	Location	No Evidence Disease (Years)	Total Duration (Years)	Status
11	Stem cell	Skin—arm	10.0	10.5	Alive
13	Stem cell	Cerv. L. N.	9.0	9.5	Alive
20	Clasmatocytic	Humerus	9.5	17.4	Alive
21	Clasmatocytic	Stomach	6.2	7.0	Alive
23	Clasmatocytic	Tibia	7.0	9.0	Alive
24	Clasmatocytic	Femur	6.1	6.3	Alive
25	Clasmatocytic	Stomach	6.0	7.0	Alive
27	Clasmatocytic	Max. antrum	3.1	3.1	Alive
30	Lymphocytic	Eye lid	8.0	8.0	Lost
32	Lymphocytic	Stomach	7.0	7.1	Alive
33	Lymphocytic	Skin—back	10.0	10.1	Alive
34	Lymphocytic	Femur	6.0	10.0	Alive
35	Lymphocytic	Parotid	3.0	11.0	Alive
36	Lymphocytic	Parotid	3.5	3.7	Alive
37	Hodgkin's	Ing. L. N.	19.0	19.1	Alive
40	Hodgkin's	Cerv. L. N.	14.8	19.0	Alive
42	Hodgkin's	Axill. L. N.	5.5	6.5	Alive (Tbc)
46	Follicular	Ing. L. N.	4.5	6.5	Dead
47	Follicular	Ing. L. N.	8.5	9.0	Alive
48	Follicular	Cerv. L. N.	7.5	8.5	Alive

Listed in Table IV are 20 cases, 18 of them still alive, one dead without evidence of lymphoma at necropsy 45 years after the excision of the primary process, and one patient lost from observation eight years after operation. Five of the patients had had local recurrence. These were treated by secondary excision in two and irradiation in three. They had had no further evidence of their disease 30, 60, 88, 95, and 148 years since the secondary procedure. Another case, although apparently free from lymphoma for five years, has been institutionalized for active pulmonary tuberculosis. The average postoperative survival for this group of 20 cases is eight years, and both the average and mean total duration nine years. They have, thus, as a group exceeded all expectations for survival, and those living are clinically apparently free of lymphoma.

DISCUSSION—It seems obvious that a blanket prohibition of surgical therapy in malignant lymphoma is unwarranted. It is equally apparent, however, that relatively few cases are susceptible to this therapeutic method. Comparatively few patients have sufficiently localized and accessible lesions when first encountered. It is of interest that among 135 necropsies upon lymphomatous individuals the lesions were completely localized in 10 per cent of the subjects.¹ This figure cannot be considered representative of the proportion of tumors which might be treated surgically since a significant number appear in inaccessible regions and not a few may remain sufficiently obscure clinically so that the need for exploration may fail to materialize. In the event that the lesion is circumscribed, reasonably limited in size and accessible technically there seems to be no factual basis for the avoidance of surgery.

The question of diagnostic biopsy as a preliminary to radical operation raises a moot point. A discussion as to whether or not the procedure may be a means of dissemination does not lie within the province of this paper. The need for biopsy arises in so many instances that it will be practiced whatever the individual opinion. Under such circumstances, however, the following observation is distinctly worthy of recognition. In a group of 33 cases with malignant lymphoma of the gastro-enteric tract only four showed metastasis to regional lymph nodes. In 16 instances lymph nodes had seemed to be the seat of metastasis at gross examination but showed only banal inflammation or hyperplasia upon microscopic examination. It is recommended therefore, that if biopsy is contemplated it should be made within the primary visceral lesion, when there is one, and not in adjacent lymph nodes even if they appear to be involved to inspection or palpation. On many occasions diagnostic biopsy has been unsuccessful when this recommendation has been ignored. It is surprising but nonetheless true that a disease so prone to rapid dissemination through the lymph node system should upon affecting a viscus primarily be less likely to spread in this manner than carcinoma in the same location.

Reference to the survival figures can permit no doubt that surgical

eradication does improve the prognostic outlook in selected cases of lymphoma^{10, 11, 12} This is most strikingly the case in the reticulum cell sarcoma group (stem cell and clasmatocytic lymphoma) Is it possible that the surgical success is apparent only and can be attributed to other factors? Since all types of malignant lymphoma comprised this series it would appear that there was no selection on a histologic basis As a matter of fact the majority of patients in this series suffered from the more malignant forms of lymphoma It is within the realm of possibility that the extranodal location of these lesions may have caused modification in the clinical course Prolonged survival of this sort has been recorded elsewhere, notably with lesions of bone and skin This is belied in part by the presence of 16 primary nodal cases in the present series and further emphasized by the fact that seven of these appeared in the so-called "cured" group (Table IV) Moreover, in an analysis of our own material there were found 31 cases with primary lymphomatous involvement of a viscus or bone which at the time of initial examination appeared to be circumscribed In contradistinction to the present group these cases were treated after biopsy by irradiation alone Although the range of survival in these extended from 0.1 to 9.3 years the average total duration was 2.1 years and the median 1.0 years The distribution and histologic nature of the lesions were similar to those in the group of surgically treated cases It would seem, then, that neither the location of a lesion nor its morphologic structure could account for the improvement of prognosis observed following radical surgery

The question of the advisability of postoperative prophylactic irradiation to the operative site cannot be answered with certainty Twenty-one cases were so treated and among these eight suffered recurrence ten had no recurrence, and in three the outcome is not known It is probably wiser to administer irradiation to those cases in which the surgeon does not feel confident that he has extirpated all foci of involvement Preoperative irradiation would seem to be pointless except in those cases in which a bulky tumor might be made more available to surgical manipulation as the result of shrinkage caused by roentgen radiation Under other circumstances it should be appreciated that irradiation can so affect a lesion as to render its histologic identification impossible or so disturb adjacent tissues as to interfere with both the surgical procedure and subsequent healing

In a disease as prone to clinical variation and in which progression may occur insidiously without overt manifestation it would be foolhardy indeed to claim that cures are effected by any means It seems reasonable to state, however, that cases judiciously selected in the manner indicated above may, if treated by radical surgery, experience far better results than might be anticipated from roentgenotherapy alone

SUMMARY AND CONCLUSIONS

1 This study concerned itself with 48 cases of malignant lymphoma of all types, with sufficient localization to permit radical surgical excision

2 Despite several deaths immediately after operation the average post-operative duration was 5 2 years and the average total duration 6 9 years

3 These figures were significantly greater than those obtained from other cases treated by irradiation alone

4 There were 20 cases without residual evidence of lymphoma including one which came to necropsy 4 5 years after operation The average total duration of these cases was nine years and the postoperative range extended from 3 to 19 years

5 It is believed that radical surgery has a very definite place in the treatment of certain cases of malignant lymphoma and that apparent freedom from the disease for long periods of time has resulted in many individuals so treated

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BRIEF COMMUNICATIONS

TRAUMATIC RUPTURE OF THE THORACIC AORTA*

CASE REPORT

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TRAUMATIC RUPTURE of the thoracic portion of the aorta is rare. Accordingly, the report of a case of almost complete rupture or tear of the thoracic aorta as a result of trauma alone, which resulted in the death of the individual is considered of interest.

Case Report—A soldier, white, male, age 36, while walking, was struck by a two and one-half ton Army truck, which threw him approximately 30 feet, killing him instantly. The body was brought to the Station Hospital, Gulfport Field, Miss., and an autopsy was performed. Inspection revealed severe injuries, as evidenced by lacerations of the skin of the right frontal region, over the bridge of the nose, upper lip, penetrating the entire thickness of the lip for two centimeters, denuded skin over the fourth and fifth knuckles of the left hand, and a compound fracture of the first phalanx of the right index finger, which was almost completely severed. On palpation, there were multiple fractures of the bones of the nose, ribs, and the middle third of the right femur. There were also linear tears of the liver and the left kidney.

There were fractures of the right ninth and left ninth and eleventh ribs. Upon removing the anterior chest plate, approximately 2000 cc of dark blood mixed with clots were found in the left pleural cavity, with associated collapse of the left lung. There was considerable hemorrhage into the mediastinum. The right lung was bloody and wet.

At the junction of the aortic arch and the thoracic aorta, there was a tear on the left side, almost completely transecting the aorta, except for a small area 1 cm in length. This undoubtedly was the cause of the hemorrhage into the mediastinum and the left pleural cavity. There was no evidence of previous disease of the aorta.

Death was due to exsanguination as a result of a traumatic rupture of the aorta with bleeding into the left thorax and mediastinum, associated with multiple fractures of the ribs, nose, right femur, and the right index finger, and lacerations of the liver and the left kidney.

DISCUSSION—Ruptures of the aorta may be classified according to etiology as follows: (1) Trauma, (2) extrinsic erosion, (3) hypoplasia, (4) coarctation, (5) inflammation, and (6) degeneration. The arch of the aorta lies in the superior mediastinum behind the lower part of the manubrium sterni. It commences behind the right margin of the sternum at its union with the second costal cartilage, and extends to the left across the trachea and then backwards, to end at the left side of the lower border of the fourth thoracic vertebra. At its commencement it has the same diameter as the ascending aorta, 28 mm (1.1 inches) but after giving

* Submitted for publication October 8, 1913

off three large branches, the diameter is reduced to 23 mm (a little less than 1 inch)²⁰ The thoracic portion of the ascending aorta lies in the posterior mediastinum, it extends from the termination of the arch, at the lower border of the left side of the fourth thoracic vertebra, to the aortic opening in the diaphragm, where opposite the twelfth thoracic vertebra, it becomes continuous with the abdominal portion Its length is from 17.5 to 20 cm (7 to 8 inches) and its diameter diminishes from 23 mm at its commencement to 21 mm at its termination²¹

From an anatomic viewpoint, it can be seen that the site of rupture of the thoracic aorta in this case is distal to the point where the major branches of the arch emerge This point of emergence represents a relatively fixed portion, whereas distal to this is a comparatively mobile portion of the thoracic aorta Thus, the point of junction of these two elements is most likely to be subjected to strain, particularly in the event of a severe, sudden blow displacing thoracic structures by force of momentum, producing either a direct or *contrecoup* injury Since there is no evidence of fracture of the ribs or sternum in the vicinity of the tear in the aorta, it must be assumed that there was no direct trauma However, the bony thorax is not a rigid structure but can be compressed both laterally and anteroposteriorly to a varying degree, depending on the age of the person and the resilience of the cartilaginous rib ends In this instance, the individual was of middle age and there was no evidence of premature calcification of the cartilages and their resilience was normal According to Waifield,²⁵ the mechanism in injuries to the heart and the proximal portion of the aorta or the root is that in full inspiration, sudden compression of the chest finds the heart caught and held between the inflated lungs A violent blow on the chest, whether over the heart or not, may injure the heart, particularly if it is in diastole It may rupture the myocardium, a valve, or the root of the aorta

Narr and Wells¹⁸ hold that the confinement of fluid in any given space depends upon two factors, *viz*, the strength of the container and the pressure exerted upon it by the confined fluid Both factors may be altered simultaneously in the human aorta Therefore, more than one important change may be present in any given case of rupture Furthermore, we must conclude, whether it can be demonstrated or not, that there has been an alteration of at least one of these forces Klotz and Simpson¹⁰ found in testing aortas of individuals between the ages of twenty and forty years that a pressure of 1000 mm of mercury was not sufficient to rupture its walls Oppenheim¹⁷ found that rupture occurred at a pressure of about 3000 mm of mercury in normal human aortas Moritz¹⁶ found that pressures of from 800 to 1200 mm of mercury induced through a cannula inserted in the proximal end of the aorta of living rabbits resulted in rupture of the portal vein or its tributaries The aorta could not be ruptured because of the rapid flow of blood through its peripheral circulation Sudden changes of pressure will have much greater effect than a continuous force Consequently, these figures are higher than those in the sudden tearing force

necessary to burst a normal aorta. This result is apparently due to the sudden transmission of the force of the blow to the confined noncompressible blood. It is interesting that in traumatic ruptures, as in ruptures due to other causes, the site of predilection is in the ascending portion of the arch and at the duct of Botalli, thus favoring either Rindfleisch's¹⁹ theory that these areas, being comparatively fixed, are predisposed to injury, or Abbott's¹ belief that the aorta may be congenitally weak in these regions.

Terrific blows to the thoracic cage have repeatedly resulted in the rupture of the aorta, which have been considered structurally normal, as cited by Rolleston,²² Busse,³ Copeland,⁴ Jaffe and Sternberg,⁷ Landau,¹¹ Kemp,⁹ and Griffiths.⁸ There are but few cases of traumatic rupture and those described have all been associated with grave thoracic injuries. Flying objects, such as blocks of wood or stone, train and automobile accidents, falls from high buildings, bridges, and airplanes, have all been found the cause of bursting the aorta. Copeland⁴ reports a case of traumatic rupture of the healthy thoracic aorta without external signs of the cause of death. A laborer, age 40, was struck by a large mass of falling earth, which gave him a glancing blow on the back, knocking him down. At postmortem, there was free blood in the peritoneal cavity and the left pleural cavity. The descending aorta was ruptured straight across, with no evidence of disease. Griffiths⁸ reports a case of traumatic rupture of the thoracic aorta in a man, age 26, who was admitted to the hospital dead, having been involved in a motorcycle accident. Autopsy showed several severe injuries and at a point beyond the origin of the great vessels there was a T-shaped rupture of the aorta with considerable extravasation of blood.

Two cases reported by Landau and Kemp are interesting. Kemp⁹ reports a case of traumatic rupture of the aorta in a male, age 45, admitted dead, with a history of having been struck on the head and chest by a portion of a stone fly wheel, which had been separated while revolving at full speed in a motor works. He had a large abrasion over the sternum. Autopsy revealed the sternum to be fractured obliquely from above downwards and backwards at the level of the third to the fourth costal cartilages. There was extravasation of blood into the anterior mediastinum. The pericardium was greatly distended with blood which had escaped from a transverse tear of the aorta, just beyond the line of the aortic valve. Landau¹¹ reported a case of rupture of the normal aorta in a woman, age 68, brought in dead, having been knocked down by a motor car. Examination of the body showed a wound of the forehead and a compound fracture of the nasal bones. There was no external sign of injury to the chest, but a quantity of clotted blood and serum was found in the pericardial cavity. This was seen to have come from a rent involving all the coats of the aorta for half its circumference, just above the coronary orifices. These two cases are examples of tears of the root of the aorta with intrapericardial bleeding.

Unquestionably, altered blood pressure plays an important rôle in rupture of the aorta. Cases of rupture of the aorta associated with chronic high

blood pressure are relatively frequent, as cited by Lifvendahl,¹² Oppenheim,¹⁷ Busse,³ Löffler,¹³ Strickland,²⁴ McLean and Fiddes,¹⁵ and many others. Research into the literature reveals records of numerous cases of rupture of the aorta secondary to disease processes, as cited by Lundberg,¹⁴ Sheldon and Dyke,²³ and Warfield.²⁵ The majority are associated with arterial disease, namely, atheroma or aneurysmal dilatation.

In considering extensive injuries of the aorta of the perforating type, the classification resolves itself into whether the injury is intrapericardial or extrapericardial. Piercing injuries of the extrapericardial portion of the thoracic aorta usually result in early death, because there is no surrounding structure, such as the pericardium, to limit the loss of blood. The infrequency of wounds of the intrapericardial part of the aorta is due to its position behind the sternum and to the fact that it is quite short. Blalock,² reports the successful suture of a wound of the intrapericardial portion of the ascending aorta of a Negro youth. There has appeared in the literature only one previous report of the successful suture of a wound of the thoracic aorta. This operation was performed by Dshanelidze,⁵ of Russia. Subsequently Elkins,⁶ in 1941, reported the successful suture of an ice-pick stab wound of the first portion of the aorta.

SUMMARY

A case of traumatic rupture of the thoracic aorta is reported, involving the junction of the arch and the descending portion of the aorta.

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RUPTURE OF THORACIC AORTA

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ERRATUM

We wish to call attention to an unfortunate oversight in the publication of the color illustrations of Dr John W Holloway's paper, "Regional Ileitis," in the September, 1943, issue of ANNALS OF SURGERY, page 329 The legends for Figures 2 and 3 were reversed

ANNOUNCEMENT

FINNEY-HOWELL RESEARCH FOUNDATION, INC

Announcement has been made by the Finney-Howell Research Foundation, Inc, that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Maryland, by January 1, 1944. Applications received after that date cannot be considered for 1944 awards, which will be made the first of March, 1944.

This Foundation was provided for in the will of the late Dr George Walker of Baltimore for the support of "research work into the cause of cancer and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of \$2000 are awarded for the period of one year, with the possibility of renewal up to three years, when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank form which will be furnished by the Secretary or any member of the Board of Directors.

October 1, 1943

At the March meeting of the Board of Directors of the Finney-Howell Research Foundation, Inc, 1211 Cathedral Street, Baltimore, Md the following annual fellowships were awarded for 1943

For the third year

Rose I Shukoff, M D, University of Petrograd To work at the Glasgow Royal Cancer Hospital, Glasgow, Scotland, under Dr P R Peacock

Emilia Vicari, M D, Ohio State University To work at the Jackson Memorial Laboratory for Cancer Research, Bar Harbor, Maine, under Dr C C Little

For the second year

Borroughs Reid Hill, M S, Tulane University To work with Dr Louis Fieser at Harvard University

New

Nelicia Maier, M D, Medical School, Paris, France To work at Yale University Medical School, New Haven, Conn, with Dr Wm T Salter

James Alexander Miller, M S, University of Wisconsin To work at the Medical School University of Wisconsin

BOOK REVIEWS

THE SEXUAL GLANDS OF THE MALE By Oswald S Lowsley, M D, Frank Hinman, M D, Donald R Smith, M D, and Robert Gutierrez, M D Oxford University Press, 619 pp, \$10 00, New York, 1943

This text is largely reprinted from the Oxford Loose Leaf Urology. The subject matter and the manner of its presentation are well known to urologists from previous writings by these well-known authors. However the present text is brought up to date and each subject is discussed thoroughly. Approximately one-half of the 619 pages are given to a detailed consideration of the seminal vesicles and vasa deferentia. Lowsley's contribution on the prostate gland comprises 191 pages of which 81 are devoted to surgical technic and illustrated by the incomparable drawings of Wm Didusch. Hinman and Smith deal largely with the clinical and pathologic features of diseases of the epididymes and testicles, surgical technic for the most part, being omitted. Some of the surgical practices advocated by Dr Lowsley might provoke considerable controversy, thus his advocacy of total perineal prostatectomy for benign prostatic hyperplasia, as a means of preventing cancer, will no doubt prove too radical for the average urologist. He continues to employ, but apparently less often, cystotomy preliminary to perineal operations upon the prostate gland, this needs no further controversial discussion. Endocrine therapy in prostatic cancer is said to bring results comparable with those reported by Huggins, no statistics are given. It is suggested that a "tuck" using ribbon catgut, be taken in the external sphincter muscle after prostatectomy to prevent urinary incontinence, elsewhere it is stated that perineal operations upon the prostate gland should not be followed by incontinence.

This section, as is true of all of Dr Lowsley's contributions, is thorough, interesting stimulating and, in some respects, original. The chapters by Hinman and Smith are entirely adequate and presented in an orderly manner, appropriate in a work of this kind. The fact that the radical operation for testicular cancer has been discarded is not so surprising as former advocacy of the procedure, based on statistical proof of its superiority over simple orchiectomy. Among the reasons given for this change of attitude is the alleged efficiency of deep roentgenotherapy which, from our experience is a weak argument. One could scarcely take exception to the thoroughness with which Gutierrez has presented his subject. However, it seems to me that the obsolete operations upon the seminal vesicles might have been described with less detail. One might question the author's advocacy of vesiculectomy for the treatment of chronic vesiculitis especially for psychotics and sexual neurasthenics. Conservative treatment is described "with the understanding that these procedures are in reality only preliminary steps leading to the main work which is always surgical."

It has long been our impression that operations upon the seminal vesicles for chronic inflammation belong largely to another era. However, this is a complete and highly valuable contribution. This volume shares with the majority of "systems" the common weakness of disregarding the relative importance of various subjects in proportioning the text. "The Sexual Glands of the Male" will undoubtedly prove valuable both as a text book and for purpose of references.

LEON HERMAN, M D

RENAL LITHIASIS Charles C Higgins, M D, Springfield, Ill, and Baltimore Md
Charles C Thomas, \$3 00, 1943

This monograph comprises 140 pages of text with 18 illustrations. Its chief value lies in a comprehensive discussion of the causes and development of urolithiasis to which 70 pages of text are given.

The author presents the results of extensive personal investigations dealing chiefly with the etiologic influences of diet. The value of these studies is in no way lessened by the fact that they are largely confirmatory of previous demonstrations by animal experimentation of the association of deficiencies in vitamins A and C with urolithiasis and kartinization in the urinary tract.

The various technics employed in chemical analyses of stones, including that favored by the author, are described. Dietary treatment is given in detail and its value estimated with commendable conservatism. This is likewise true of the discussion of the various local methods used in the attempt to dissolve stones. With the exception of cystin and soft alkaline stones, successes have been few.

The author, as did Crowell, succeeded in dissolving a cystin kidney stone. Dr. Higgins notes recurrence of stone following administration of a high protein diet, this is the usual result in cystinurics who are on a normal diet.

This monograph is well worth the attention of specialists and practitioners alike.
LEON HERMAN, M.D.

OBSTETRICAL PRACTICE By Alfred C. Beck, M.D., 3rd ed. 6 $\frac{7}{8}$ x 10, xi + 938 pp., 1064 figs. \$7.00. Baltimore: Williams & Wilkins Co., 1942.

This 3rd edition of the book reveals considerable improvement over both former editions. First, extensive revision of much of the original text, the addition of considerable entirely new and up-to-date material, plus more and better illustrations, of which there are 1100, make it a more complete textbook of obstetrics. An author is indeed fortunate who can draw his own pictures, even though he may not be a skilled artist. This is particularly evident in Beck's "Obstetrical Practice."

Parenthetically, and perhaps not the least important, is the excellent "architecture" and reasonable price of the book. The publishers, The William & Wilkins Co., Baltimore, are to be congratulated. It is no simple job, under existing conditions, to publish a textbook of this character and size, containing 1100 illustrations, many in color, and keep the price down to prewar levels.

Throughout this 3rd edition, the author has kept the undergraduate student as well as the practitioner in mind, "adding and subtracting" such material as would make for completeness, readability and up-to-the-minute information. Among the outstanding chapters, might be mentioned those on prenatal care, the mechanism of labor, posterior positions of the occiput, breech presentation, forceps and cesarian section, including the technic of local infiltration anesthesia. Furthermore, the revised and more complete index adds materially to the convenience and usefulness of this edition.

It is unfortunate that the author does not use the classification of the toxemias of pregnancy as advocated by the American Committee on Maternal Health. Indeed, he does not give any classification of the toxemias, which in view of the rather generous use of tabulations and groupings throughout the book—a very excellent plan—seems rather strange. Except for this omission, this chapter forms another outstanding section of the book.

Again, wherever the treatment of hemorrhage and/or shock comes up for discussion, there is no mention made of the use of plasma. Since plasma is now so successfully used early in all such cases, and in most instances long before transfusion can be accomplished, it would seem that such an important life-saving agent should have been recommended.

The importance of anesthesia in obstetrics cannot be overemphasized. Poor anesthesia remains a very potent cause of obstetric deaths. Except for chloroform and local infiltration anesthesia, it would seem that the author has not given this subject as much attention as it deserves. Fractional spinal or continuous caudal are not discussed.

The tabulation of an excessive number of references does not materially enhance the

value of a teaching text but it does require many additional pages which add to the bulk of the book. We suggest, in keeping with the compactness of the text, that fewer references generally, and better distribution specifically, would keep the book thoroughly modern without detracting from its usefulness.

It may well be said that in Beck's "Obstetrical Practice," 3rd Edition, the undergraduate student, the general practitioner, or the specialist has a conservative, concise, readable and practical textbook, splendidly illustrated, and at a price that anybody's budget can stand. No one except a good, "seasoned" teacher could have produced such a book. We predict an increase in its popularity.

HARVEY B. MATTHEWS, M.D.

ACUTE INFECTIONS OF THE MEDIASTINUM By Harold Neuhof, M.D., and Edward Jemerin, M.D. Baltimore: Williams and Wilkins Co., 6 x 9, vii + 407 pp., 157 figs. \$6.00. 1943.

Acute Infections of the Mediastinum, by Neuhof and Jemerin, is destined to fill a long neglected gap in our knowledge of acute mediastinitis. Although there is a mass of literature on this subject, no complete text has heretofore been produced.

This book is unique in its originality in both its method of presentation and the source of its data. It is entirely free from the chauvinistic tendency which so frequently invades texts on medical subjects. While the knowledge and facts of the past are reviewed in the introduction, the text proper contains only the data collected by the authors from their carefully studied clinical material in Mount Sinai Hospital.

The subject is presented by recording one hundred case reports which, for purposes of systematic presentation, have been divided into four groups on an etiologic basis. Anatomic subdivisions have not been emphasized by anatomic pus pockets and planes of spread are easily visualized by the drawings which accompany the case reports.

This book is so well expressed that it makes it possible for us to see and hear with the authors. It apparently was not produced for any one medical group. The specialist will find an eleemosynary granary to increase his superior knowledge. To the roentgenologist is given excellent reproductions of actual roentgenologic findings, with precise and replete word-pictures of these studied cases and, as the roentgenograms are frequently the only, or, at least, the most essential means of positive diagnosis, he will find much of interest. To the medical diagnostician, the thoracic and general surgeon, this text is indispensable. It calls attention to the fact that although mediastinitis is generally believed to be a rarity, that, in reality, it is comparatively common. This text will surely stimulate general interest in the subject of mediastinitis and make early diagnosis more common. It will help materially in making a differential diagnosis between actual suppurative mediastinitis, which demands early surgical intervention, and the more benign variety mediastinal lymphadenitis or cellulitis, which may subside with conservative treatment.

The text, as above stated, consists of one hundred case reports. The cases range from the comparatively simple cervical retro-esophageal abscess, the etiologic factor being a puncture wound of the esophagus from a chicken bone, to the most complicated types. Case 81 presents such a picture. Here is presented an apparently simple cervical abscess. It was, however, complicated by a spread to the mediastinum, a contralateral cervical abscess, an involvement of both lungs, bronchiectasis, and extensions to lumbar spaces. This case is so fascinatingly presented by excellent word-picture, roentgenogram reproductions, both plain and following introduction of iodized oil, that the reader not only follows the disease process but also reviews the surgical anatomy of the neck, the normal planes of spread to the mediastinum, the lumbar space, and the unusual involvement of the bronchial tree producing a bilateral bronchiectasis. The report then leads the surgeon through numerous bold, courageous, but well planned,

operative procedures Here, the surgeon sees, feels and even smells with the authors as they progress with careful surgical technic and sound surgical judgment, unroofing the intricate abscess pockets through a deep opening in the mediastinal structures and giving external drainage to these pus-containing spaces, resulting in ultimate cure

The unusual retrograde spread is also shown, as in Case 91, by acute gangrenous appendicitis, with perforation, appendectomy, with drainage, wound infection to retroperitoneum, with retroperitoneal phlegmon, extension upward with mediastinal phlegmon, bilateral pleurisy and pericarditis

The three following case reports well illustrate that this text is of interest to the entire medical profession Case 18 starts with otitis media, mastoidectomy, positive blood culture and metastatic mediastinal abscess Case 50, bronchopneumonia, non-suppurative mediastinal lymphadenitis, with spontaneous recovery Case No 34, tonsillitis and pharyngitis, cervical lymphadenitis, rheumatic fever, mediastinal lymphadenitis

Interspersed through the text are numerous simplified tables, so that, "he who runs may read" Data may be easily compiled such as etiologic factors, the most common symptoms, the reliability of roentgenogram diagnosis, the type of organism most frequently found, the pathology and pathogenesis, relationship to pneumonia, empyema and putrid and nonputrid lung abscess, the frequency in age and sex, the morbidity and mortality These tables are truly time-saving and thought provocative

After the case presentations the chapter on Fundamental Considerations is of special interest In the chapter Subclassifications, discussions of various groups of cases both suppurative and nonsuppurative are presented

The chapter on Clinical Considerations, in which history, symptoms and signs are detailed, is well written It distinguishes between, and emphasizes signs and symptoms in, the traumatic and nontraumatic, between advanced cases and those in the earlier stages The significance of hemoptysis, carcinoma and upper respiratory infections are a few of the intensely interesting details that are mentioned with references to specific case reports in the main text

The final chapter, devoted to Treatments and Results, brings this book to a satisfactory climax It is didactic but not dogmatic Facts are presented and logical explanations given, yet the reader is permitted to reach his own conclusions from unquestionable text data Operative procedures are described Unsatisfactory approaches and treatment are freely criticized Many autopsy records are recorded The whole book is stimulating It contains a complete bibliography and index of cases and is, therefore, adapted to the reference of both the general practitioner and specialist

JOHN V BOHRER, M D

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INDEX TO VOLUME 118

A

- ABBOTT, KENNETH H Metastasizing Intracranial Tumors, 343
 Abdomen, Gunshot Wounds of the, 780
 Abscess of the Lung, Acute Putrid, 656
 Absorbable Cotton, Paper and Gauze, 116
 ACKMAN, DOUGLAS Planned Timing in the Treatment of Wounds and Infections by Means of Infrequent Occlusive Dressings, 921
 Acute Postoperative Necrosis of the Liver, 149,
 Putrid Abscess of the Lung, 656
 ADAMS, RAYMOND D Changes in Brain Volume and Blood Content After Experimental Concussion, 619
 ADDENDUM 750
 Adrenal Cortical Extract, Further Experiences with the Use of, in Burn Shock, 982
 Advances in Spinal Anesthesia, 971
 ALLEN, ARTHUR W Thrombosis and Embolism, 728
 ALTEMEIER, W A Peroxide Ointments, 741
 American Surgical Association, Transactions of the, 161
 Amino Acids, Serum and Plasma in the Replacement Therapy of Fatal Shock Due to Repeated Hemorrhage, 225
 Amputation Neuroma in Nerves Implanted in Bone, 1052
 Amylase, Serum, Use in Acute Trauma to the Pancreas, 594
 Analgesia, Continuous Caudal in Surgery, 945
 ANDRUS, WILLIAM DEWITT Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, 499
 Anesthesia, Advances in Spinal, 971, (Ether and Cyclopropane) Effects of, Upon the Renal Function in Man, 717, Convulsions during General, 130
 Aneurysm Cured by Cellophane Fibrosis, Subclavian, 478
 Animal Experiments with Trinitic Acid, 417
 ANNOUNCEMENT Finney Howell Research Foundation, Inc, 1076
 Anterior Root Stimulation, Effect on Sympathetic Nerves to Pupil and Upper Extremity, 647, Sacral Meningocele, 913
 Aorta, Traumatic Rupture of the Thoracic, 1071
 ARIEL, IRVING Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract, 366
 Arteries, Coronary, Communications Between, Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34

B

- BAKER, ROGER DENIO Animal Experiments with Trinitic Acid, 417

- BARCHAM, I S The Coagulability of Venous Blood of Normal and Diseased Legs, 482
 BARGEN, J ARNOLD The Spread of Carcinoma of the Rectum Invasion of Lymphatics, Veins and Nerves, 76
 BARSKY, ARTHUR I, MAJ Use of One Flap to Restore Extensive Losses of the Middle Third of the Face, 988
 Basic Principles in the Treatment of Thermal Burns, 187
 Battle Wounds of the Head, Experiences with, 1
 BECK, CLAUDE S Communications between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34, Principles Underlying the Correct Approach to the Treatment of Myocardial Ischemia, 788
 Beck Operation, Clinical Appraisal of the, 807
 Bed Sores, Protein Metabolism and, 1015
 BENSON, RAYMOND Nonneoplastic Diverticula of the Jejunum and Ileum 377
 Bladder, Primary Osteogenic Sarcoma of the, 887
 BLADES, BRIAN Conservation of Lung Tissue by Partial Lobectomy, 353
 Blood of Normal and Diseased Legs, The Coagulability of Venous, 482
 Blood Vessels, Tumor of, Featuring Vascular Endothelial Cells, Hemangioendothelioma, 44
 BOHRER, JOHN V Review of Acute Infections of the Mediastinum, 1079
 BOLDREY, EDWIN Amputation Neuroma in Nerves Implanted in Bone, 1052
 Bone, Amputation Neuroma in Nerves Implanted in, 1052
 Bones, The Choice of Operation for Delayed and Nonunion of Long, 665
 BOOK REVIEWS Abdominal and Genito-Urinary Injuries Military Surgical Manuals III, National Research Council, Reviewed by Walter Estell Lee, 488, Acute Infections of the Mediastinum Reviewed by John V Bohrer, 1079, Endoscopic Prostatic Surgery Reviewed by Thomas J Kirwin, 920, First Aid, Surgical and Medical Reviewed by William V Healey, 488, The Hemorrhagic Disorders and The Physiology of Hemostasis Reviewed by Leandro M Tocantins, 487, Obstetrical Practice Reviewed by Harvey B Matthews 1078 Renal Injuries Reviewed by Leon Herman 1077 The Sexual Glands of the Male Reviewed by Leon Herman, 1077
 BOYS, FLOYD Experimental Studies on Peritoneal Adhesions Fourth Report—Subperitoneal and without Heparin, 612
 Brain Volume and Blood Content After Experimental Concussion Changes in, 619
 Breast Amputation Skin Re-attachment, 1071

- Breast, Carcinoma of the II—Criteria of Operability, 859, (continued), 1032
 BROOKS, JOHN R Changes in Brain Volume and Blood Content After Experimental Concussion, 619
 BROWDER, NEWTON C Problems of Protein Nutrition in Burned Patients, 215
 BRUCKNER, JOHN P Strik Wound of the Heart, 46
 BURCH, JOHN C Pilaridal Cysts and Sinuses, 706
 Burns, Basic Principles in the Treatment of, 187, A Clinical Test for Differentiating Second from Third Degree Burns, 427, Liver Necrosis in, 402, The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and, 171, Surface Treatment of, 761
 Burn Shock, Further Experiences with the Use of Adrenal Cortical Extract in, 982, Particular Reference to Experimental Hemorrhage and Gelatin as a Plasma Substitute 193
 BUTT, HUGH R Management of Ulcers Among Naval Personnel 489

C

- CAMPBELL, KENNETH N Effects of Ether and Cyclopropane Anesthesia Upon the Renal Function in Man, 717
 Cancer of the Gastro Intestinal Tract, Metabolic Studies in Patients with, 366
 Carcinoma of the Breast II—Criteria of Operability, 859, (continued), 1032, of Duodenum, 838, of the Hyperplastic Thyroid, A New Concept Regarding the Origin of so called Primary, 843, Pancreatectomy for, 603
 Caudal Analgesia, Continuous, in Surgery, 945
 Cellophane Fibrosis, a Subclavian Aneurysm Cured by, 478
 Cells, A Tumor of Blood Vessels Featuring Vascular Endothelial, Hemangio Endothelioma, 445
 CHANDY, JACOB A Subclavian Aneurysm Cured by Cellophane Fibrosis, 478
 Changes in Brain Volume and Blood Content After Experimental Concussion, 619
 CHILDS, CHARLES G, III Carcinoma of Duodenum, 838
 Choice of Operation for Delayed and Nonunion of Long Bones, 665
 Cholecysto Enterostomy, Choledocho-Enterostomy and Entero Enterostomy by Means of Rubber Bands The Use of Rubber Bands in the Mikulicz Operation, 558
 Choledocho Enterostomy, Entero Enterostomy, and Cholecysto-Enterostomy by Means of Rubber Bands, 558
 Choledochus Cyst, 91
 Clinical Appraisal of the Beck Operation, 807
 Clinical Test for Differentiating Second from Third Degree Burns, 427
 CLOWFS, GEORGE H A, JR The Surface Treatment of Burns, 761
 Coagulability of Venous Blood of Normal and Diseased Legs 482
 COLEY BRAOLEY L Experiences of a Surgical Consultant of a Service Command, 751

- COLLER, FREDERICK A Effects of Ether and Cyclopropane Anesthesia Upon the Renal Function in Man, 717
 COLLINS, VINCENT P The Peptic Ulcer and Chronic Gastritis, 1005
 COLP RALPH Gastric Histology and Subtotal Gastrectomy 523
 Communications Between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34
 Compound Fractures, Surgical Principles Opposed to "Rule of Thumb" in the Treatment of, 305, and Burns, The Study of the Prevention of Infection in Contaminated Accidental Wounds 171
 Concussion, Changes in Brain Volume and Blood Content after Experimental, 619
 Congenital Duodenal Obstruction, 372
 CONNELL, F GREGORY Partial Fundusectomy (Proximal Gastrectomy), 1000
 Conservation of Lung Tissue by Partial Lobectomy, 353
 Contaminated Accidental Wounds, Compound Fractures and Burns, The Study of the Prevention of Infection in, 171
 Continuous Caudal Analgesia in Surgery, 945
 Co Tui The Coagulability of Venous Blood of Normal and Diseased Legs, 482, Protein Metabolism and Bed Sores, 1015
 Convulsions during General Anesthesia, 130
 CORCORAN, A C Immediate Effects on Renal Function of the Onset of Shock due to Fracture Occluding Limb Tourniquets, 871
 Coronary Arteries, Communications between, Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34
 CORRECTION 1080
 CRAIG, W M Wounds of the Central Nervous System, 635
 CRANE, A R Primary Osteogenic Sarcoma of the Bladder, 887
 Cystic Duct Drainage, routine following Cholecystectomy, 97
 Cysts of the Popliteal Space, Synovial Clinical Significance and Treatment, 438, (Pilaridal) and Sinuses, 706, Solitary, or Cyst like Structures, of Pulmonary Origin, the Surgical Management of, 50

D

- DANDY, WALTER E Recent Advances in the Treatment of Ruptured (Lumbar) Intervertebral Disks, 639
 DAVIO, VERNON C The Importance of Fundamentals in Surgical Education 161
 DAVIES, A J M Massive Fibroma of the Sculp, 154
 DAVIDSON, CHARLES S Problems of Protein Nutrition in Burned Patients, 215
 DECOURCY, JOSEPH L Dermoid Cyst of Pancreas, 394
 Diabetes Mellitus, Results of Gallbladder Surgery in, 107
 DINGWALL, JAMES A, 31d A Clinical Test for Differentiating Second from Third Degree Burns, 427

- Distribution of the Sympathetic Nerves to the Pupil and Upper Extremity as Determined by Stimulation of the Anterior Roots in Man 647
- DIXON, CLAUDE F. Nonneckerian Diverticula of the Jejunum and Ileum, 377
- DONALDSON, GORDON A. Thrombosis and Embolism, 728
- DOUBILET, H. The Coagulability of Venous Blood of Normal and Diseased Legs, 482
- DRASTEDT, LESTER R. Some Physiologic Problems in Surgery of the Pancreas, 576
- Drainage, Routine Cystic Duct, Following Cholecystectomy, 97
- DRISCOLL, ROBERT E. Thyrocardiac Disease, 681
- Duct, Cystic, Routine Drainage, Following Cholecystectomy, 97
- DUNHAM, CHARLES LITTLE. Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut), 288, Surgical Gut (Catgut) Tubing Fluid as a Tissue Irritant, 269
- DUNLOP, GEORGE, LIEUT. Sphenous (Ligation) Resection in the Obese, 1024
- Duodenal Obstruction, Congenital 372
- Duodenum, Carcinoma of, 838

E

- Effect on Gastric Acidity of Gastro Enterostomy and Gastric Resection for Peptic Ulcer, 551
- Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, 499
- EISELE, HAROLD E. Results of Gallbladder Surgery in Diabetes Mellitus, 107
- ELKIN, DANIEL C., LT. COL. Gunshot Wounds of the Abdomen, 780
- ELMAN, ROBERT. Amino Acids, Serum and Plasma in the Replacement Therapy of Fatal Shock Due to Repeated Hemorrhage, 225
- Embolism and Thrombosis, 728
- Endothelial Cells, A Tumor of Blood Vessels Featuring Vascular Hemangio Endothelioma 445
- Enterio Enterostomy, Cholecysto Enterostomy, and Choledochostomy by Means of Rubber Bands, 558
- ERRATUM 750
- Ether and Cyclopropane Anesthesia, Effects of, Upon the Renal Function in Man, 717
- Experiences of a Surgical Consultant of a Service Command, 751, with Battle Wounds of the Head, 1
- Experimental Studies on Peritoneal Adhesions—Fourth Report—Sulfonamides with and without Heparin, 612
- Experiments with Tannic Acid, Animal, 417

F

- Face Use of One Flap to Restore Extensive Losses of the Middle Third of the Face, 988
- FEIL, HAROLD. Clinical Appraisal of the Beck Operation, 807
- FERGUSON, CHARLES H. Advances in Spinal Anesthesia, 971
- Fibroma of the Scalp Massive 154

- Fibrosis a Subclavian Aneurysm Cured by Cellophane 478
- FINE, JACOB. Traumatic Shock 238
- Fixation for Fractures of the Sternum a Method of, 158
- Flap, Use of One Flap to Restore Extensive Losses of the Middle Third of the Face, 988
- Fluids Hydrocarbon Content of Nonboilable Surgical Gut Tubing 285
- Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut), Irritant Properties of Tubing 288
- Fractures and Burns the Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound 171, of the Sternum A Method of Fixation for, 158, Surgical Principles Opposed to "Rule of Thumb" in the Treatment of Compound, 305
- FRANTZ, VIRGINIA KNEELAND. Absorbable Cotton, Paper and Gauze, 116
- Fundusotomy, Partial, (Proximal Gastrectomy) 1000
- Further Experiences with the Use of Adrenal Cortical Extract in Burn Shock 982

G

- GAIL, EDWARD, MAJ. The Surgical Treatment of Malignant Lymphoma, 1064
- Gallbladder Surgery in Diabetes Mellitus, Results of, 107
- Gallstone, Intestinal Obstruction due to a, 101
- Gastrectomy, Gastric Histology and Subtotal, 523
- Gastrectomy, Total, by the Transthoracic Approach 816
- Gastric Histology and Subtotal Gastrectomy, 523
- Gastric Secretion, Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on, 499
- Gastritis The Peptic Ulcer and Chronic, 1005
- Gastro Enterostomy and Gastric Resection for Peptic Ulcer, Effect on Gastric Acidity of, 551
- Gastrointestinal Tract Metabolic Studies in Patients with Cancer of the, 366
- Gelatin is a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, 193
- Gelatin, Intravenous, 1058
- GEORGE, WILLIAM A. Observations on the Distribution of the Sympathetic Nerves to the Pupil and Upper Extremity as Determined by Stimulation of the Anterior Roots in Man, 647
- GITLITZ, ABRAHAM J. Gastric Histology and Subtotal Gastrectomy, 523
- GOFTSCH, EMIL. A New Concept Regarding the Origin of so called Primary Carcinoma of the Hyperplastic Thyroid 843
- GOLDTHWAIT, JOEL C. Changes in Brain Volume and Blood Content After Experimental Concussion, 610
- Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, Effects of Pedicle, 499
- GRAY, HOWARD K. Congenital Duodenal Obstruction, 372
- Gunshot Wounds of the Abdomen 780
- GUILD, FRANK B. Planned Timings in the Treatment of Wounds and Infections by Means of Infrequent Occlusive Dressings 921

Gut, (Catgut), Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical, 288
Gut Tubing Fluids, Hydrocarbon Content of Nonboilable Surgical, 285

H

HAAUGENSEN, C D Carcinoma of the Breast II—Criteria of Operability, 859, (continued), 1032
HAGGART, G E Synovial Cysts of the Popliteal Space Clinical Significance and Treatment of, 438
HANDLER, PHILIP Animal Experiments with Tannic Acid, 417
HARRISON, PAUL W A Subclavian Aneurysm Cured by Cellophane Fibrosis, 478
HARTMAN, F W Liver Necrosis in Burns, 402
Head, Experiences with Battle Wounds of the
HEALEY, WILLIAM V Review of First Aid, Surgical and Medical, 488
Heart, Communications Between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the, 34
Heart, Stab Wound of the, 46
Hemangio Endothelioma A Tumor of Blood Vessels Featuring Vascular Endothelial Cells 445
Hemangioma of Skeletal Muscle, Venous 465
Hematogenous Osteomyelitis, The Medical Treatment of, 318
Hemorrhage, Amino Acids, Serum, and Plasma in the Replacement Therapy of Fatal Shock Due to Repeated, 225, and Burn Shock, Particular Reference to Experimental Gelatin as a Plasma Substitute, 193
HERMAN, LEON Review of Sexual Glands of the Male, 1077, Review of Renal Lithiasis, 1077
HEUER, GEORGE J The Effect on Gastric Acidity of Gastro Enterostomy and Gastric Resection for Peptic Ulcer, 551
HINGSON, ROBERT A Advances in Spinal Anesthesia, 971, Continuous Caudal Analgesia in Surgery, 945
HINSEY, JOSEPH C Observations on the Distribution of the Sympathetic Nerves to the Pupil and Upper Extremity as Determined by Stimulation of the Anterior Roots in Man, 647
HOLLOWAY, JOHN W Regional Ileitis, 329
HOLMAN, CRANSTON The Effect on Gastric Acidity of Gastro Enterostomy and Gastric Resection for Peptic Ulcer, 551
HORSLEY, J SHELTON Cholecysto Enterostomy, Choledcho Enterostomy, and Entero Enterostomy by Means of Rubber Bands The Use of Rubber Bands in the Mikulicz Operation, 558
HORSLEY, GUY WINSTON Cholecysto Enterostomy, Choledcho Enterostomy, and Entero Enterostomy by Means of Rubber Bands The Use of Rubber Bands in the Mikulicz Operation, 558
HURWITZ, ELLIOTT Acute Putrid Abscess of the Lung, 656
HURVITZ, LEWIS M Thyrocardiac Disease, 681
Hydrocarbon Content of Nonboilable Surgical Gut Tubing Fluids, 285
Hyperplastic Thyroid A New Concept Regarding the Origin of so-called Primary Carcinoma of the 843

I

Ileitis, Regional, 329
Immediate Effects on Renal Function of the Onset of Shock due to Partially Occluding Limb Tourniquets, 871
Importance of Fundamentals in Surgical Education, 161
Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, the Study of the Prevention of, 171
Infections, Planned Timing in the Treatment of Wounds and, by Means of Infrequent Occlusive Dressings, 921
Intestinal Obstruction due to a Gallstone, 101
Intervertebral (Lumbar) Disks, Recent Advances in the Treatment of Ruptured, 639
Intracranial Tumors, Metastasizing, 343
Intravenous Gelatin, 1058
IOB, VIRVIA L Effects of Ether and Cyclopropane Anesthesia upon the Renal Function in Man, 717
Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut) 288
Irritant, Surgical Gut (Catgut) Tubing Fluid as a Tissue, 269
Ischemia Principles Underlying the Operative Approach to the Treatment of Myocardial, 788

J

Jejunum in the Wall of the Stomach on Gastric Secretion, Effects of Pedicle Grafts of, 499
JENNINS, HILGER PERRY Surgical Gut (Catgut) Tubing Fluid as a Tissue Irritant, 269, Irritant Properties of Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut) 288
JOHNSTON, CARTER D Intravenous Gelatin, 1058

K

KEY, J ALBERT The Choice of Operation for Delayed and Nonunion of Long Bones, 665
KIRWIN, THOMAS J Review of Endoscopic Prostatic Surgery, by, 920
KLEINSASSER, LEROY J, CAPT Traumatic Rupture of the Thoracic Aorta, 1071
KOOP, C E Gelatin as a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, 193

L

LAHEY, FRANK H Thyrocardiac Disease, 681
LEE, WALTER ESTELL Review of Abdominal and Genito Urinary Injuries, 488, Further Experiences with the Use of Adrenal Cortical Extract in Burn Shock, 982
Legs The Coagulability of Venous Blood of Normal and Diseased, 482
LEHMAN, EDWIN P Experimental Studies on Peritoneal Adhesions Fourth Report—Sulfonamides with and without Heparin, 612
LESSER, ALBERT Intestinal Obstruction due to a Gallstone 101

- LEVENSEN, STANLEY M Problems of Protein Nutrition in Burned Patients, 215, The Surface Treatment of Burns, 761
- LEVINE, MAX Pilonidal Cysts and Sinuses, 706
- LIGHT, RUDOLPH A Venous Hemangioma of Skeletal Muscle, 465
- Limb Tourniquets, Partially Occluding, Immediate Effects on Renal Function of the Onset of Shock due to 871
- LINTON, ROBERT Thrombosis and Embolism, 728
- LISCHER, CARL E Amino Acids, Serum and Plasma in the Replacement Therapy of Fatal Shock due to Repeated Hemorrhage, 225
- Liver, Acute Postoperative Necrosis of the, 149, Necrosis in Burns, 402, Spontaneous Rupture of, Complicating Pregnancy, 396
- Lobectomy, Conservation of Lung Tissue in Partial, 353
- LOCKWOOD, J S Gelatin as a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, 193
- LORD, JERE W, JR Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, 499
- Losses of the Middle Third of the Face, Use of One Flap to Restore Extensive, 988
- LUND, CHARLES C The Surface Treatment of Burns, 761
- Lung, Acute Putrid Abscess of the, 656, Tissue, Conservation of, Partial Lobectomy, 353
- Lymphatics, Veins and Nerves, Invasion of the, in the Spread of Carcinoma of the Rectum, 76
- Lymphoma, The Surgical Treatment of Malignant, 1064

M

- MACDONALD, DEAN Routine Cystic Duct Drainage following Cholecystectomy, 97
- Malignant Lymphoma, Treatment of, Surgical, 1064
- Management of Ulcers among Naval Personnel, 489
- MARR, JEROME Venography, 469
- MARSHALL, VICTOR F Convulsions During General Anesthesia, 130
- Massive Fibroma of the Scalp, 154
- MATTHEWS, HARVEY B Review of Obstetrical Practice, 1078
- MCCONNELL, LORNE H Massive Fibroma of the Scalp, 154
- MCCORALE, H J The Recognition and Management of Acute Trauma to the Pancreas With Particular Reference to the use of the Serum Amylase Test, 594
- MCCUTCHEON, GEORGE T Pilonidal Sinus, 430
- McKIM, L H A Method of Fixation for Fractures of the Sternum, 158
- Medical Treatment of Hematogenous Osteomyelitis, 318
- MELENEY, IRVING L The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, 171
- Meningioma, 909
- Meningocele, Anterior Sacral, 913
- Metabolic Studies in Patients with Cancer of the Gastro Intestinal Tract, 366

- Metabolism, Protein, and Bed Sores, 1015
- Metastasizing Intracranial Tumors, 343
- Method of Fixation for Fractures of the Sternum, 158
- MONEY, R A Experiences with Battle Wounds of the Head, 1
- MORLOCK, CARL G Congenital Duodenal Obstruction, 372
- MOYER, CARL A Effects of Ether and Cyclopropyl Anesthesia upon the Renal Function in Man, 717
- MULHOLLAND, JOHN H Protein Metabolism and Bed Sores, 1015
- MURRAY, CLAY RAY Surgical Principles Opposed to "Rule of Thumb" in the Treatment of Compound Fractures, 305
- Muscle, Venous Hemangioma of Skeletal, 465
- Myocardial Ischemia, Principles Underlying the Operative Approach to the Treatment of, 788

N

- NAFFZIGER, HOWARD C The Recognition and Management of Acute Trauma to the Pancreas With Particular Reference to the use of the Serum Amylase Test, 594
- Necrosis in Burns, Liver, 402, of the Liver Acute Postoperative, 149
- NELSON, T Y Experiences with Battle Wounds of the Head, 1
- Nerves Implanted in Bone, Amputation Neuroma in, 1052
- Nervous System in Shock, Role of the, 256
- NEUMER, HAROLD Acute Putrid Abscess of the Lung, 656
- Neuroma in Nerves, Amputation, Implanted in Bone, 1052
- Neurosurgery, The Use of Thrombin on Soluble Cellulose in, 127
- NITAIN, ROBERT LEWIS Intestinal Obstruction due to a Gallstone, 101
- Nutrition in Burned Patients, Problems of Protein, 215

O

- Obese, Saphenous (Ligation) Resection in the, 1024
- Obstruction, Congenital Duodenal, 372
- Obstruction, Intestinal, due to a Gallstone, 101
- Occlusive Dressings, Planned Timing in the Treatment of Wounds and Infections by Means of Infrequent, 921
- Ointments, Peroxide, 741
- Operability, II—Criteria of, in Carcinoma of the Breast, 859, (continued), 1032
- Operative Approach to the Treatment of Myocardial Ischemia, Principles Underlying the, 788
- Osteogenic Sarcoma of the Bladder, Primary, 887
- Osteomyelitis, The Medical Treatment of Hematogenous, 318

P

- PACK, G T Metabolic Studies in Patients with Cancer of the Gastro Intestinal Tract, 366
- PAGE, IRVING H Immediate Effects on Renal Function of the Onset of Shock due to Partially Occluding Limb Tourniquets 871

- PALMER, LOUIS A Advances in Spinal Anesthesia, 971
- Pancreatectomy for Carcinoma, Total, 603
- Pancreas, Recognition and Management of Acute Trauma to the With Particular Reference to the use of the Serum Amylase Test, 594, Some Physiologic Problems in Surgery of the, 576
- PARKINS, W M Gelatin as a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock 193
- Partial Fundusectomy (Pilonidal Gistrectomy), 1000
- Partially Occluding Limb Tourniquets, Immediate Effects on Renal Function of the Onset of Shock due to, 871
- Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretions Effects of, 499
- Peptic Ulcer and Chronic Gastritis, 1005 The Effect on Gastric Acidity of Gastro Enterostomy and Gastric Resection for, 551
- Peritoneal Adhesions, Experimental Studies on, Fourth Report—Sulfonamides with and without Heparin, 612
- Peroxide Ointments, 741
- PHENISTER, DALIAS B Role of the Nervous System in Shock, 56
- Physiologic Problems in Surgery of the Pancreas, some, 576
- PILCHER, COBB Meningioma, 909
- Pilonidal Cysts and Sinuses, 706
- Pilonidal Sinus, 430
- Planned Timing in the Treatment of Wounds and Infections by means of Infrequent Occlusive Dressings, 921
- Plasma in the Replacement Therapy of Fatal Shock due to Repeated Hemorrhage, Amino Acids, Serum and, 225
- Plasma Substitute, Gelatin as a, with Particular Reference to Experimental Hemorrhage and Burn Shock, 193
- Popliteal Space, Synovial Cysts of the Clinical Significance and Treatment, 438
- Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, the Study of, 171
- Primary Carcinoma of the Hyperplastic Thyroid, A New Concept Regarding the Origin of so called, 843
- Primary Osteogenic Sarcoma of the Bladder, 887
- Principles Underlying the Operative Approach to the Treatment of Myocardial Ischemia, 788
- Problems of Protein Nutrition in Burned Patients, 215
- Protein Metabolism and Bed Sores, 1015
- Protein Nutrition in Burned Patients, Problems of, 215
- Pulmonary Origin the Surgical Management of Solitary Cysts or Cyst like Structures of, 50
- Pupil and Upper Extremity, Sympathetic Nerves to, 647
- PURNAM, TRACY J The use of Thrombin on Soluble Cellulose in Neurosurgery, 127
- R
- RADEMAKER LEE Spontaneous Rupture of Liver Complicating Pregnancy, 396
- RAY, BROOKSON S Convulsions During General Anesthesia, 130, Observations on the Distribution of the Sympathetic Nerves to the Pupil and Upper Extremity as Determined by Stimulation of the Anterior Roots in Man, 647
- Reactions Observed With Surgical Gut (Catgut), Irritant Properties of Tubing Fluids as a Factor in the Tissue, 288
- Recent Advances in the Treatment of Ruptured (Lumbar) Intervertebral Disks, 639
- Recognition and Management of Acute Trauma to the Pancreas, With Particular Reference to the Use of the Serum Amylase Test 594
- REES, VINCENT L Effects of Ether and Cyclopropyl Anesthesia upon the Renal Function in Man, 717
- Regional Ileitis, 329
- REID, MONT R Peroxide Ointments, 741
- REFKINS, PAUL E Metabolic Studies in Patients with Cancer of the Gastro Intestinal Tract, 366
- Renal Function, Immediate Effects on, Resulting from Onset of Shock due to Partially Occluding Limb Tourniquets, 871
- Resection, Saphenous (Ligation) in the Obese, 1024
- Results of Gallbladder Surgery in Diabetes Mellitus, 107
- RICHARDS, VICTOR Anterior Sacral Meningocele, 913
- RIFKEL, C Gelatin as a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, 193
- RHOADS, C P Metabolic Studies in Patients with Cancer of the Gastro Intestinal Tract, 366
- RHOADS, JONATHAN E Further Experiences with the use of Adrenal Cortical Extract in Burn Shock, 982
- ROBERTSON, D E The Medical Treatment of Hematogenous Osteomyelitis, 318
- ROCKEY, EUGENE W Total Pancreatectomy for Carcinoma, 603
- RODMAN, J STEWART Skin Removal in Radical Breast Amputation, 694
- Role of the Nervous System in Shock, 256
- ROMENCE, H L Liver Necrosis in Burns, 402
- Routine Cystic Duct Drainage following Cholecystectomy, 97
- Rupture of Liver Complicating Pregnancy, Spontaneous, 396
- Ruptured (Lumbar) Intervertebral Disks, Recent Advances in the Treatment of, 639
- S
- Sacral Meningocele, Anterior, 913
- SALTONSTALL, HENRY Further Experiences with the use of Adrenal Cortical Extract in Burn Shock, 982
- Saphenous (Ligation) Resection in the Obese, 1024
- Sarcoma, Primary Osteogenic, of the Bladder, 867
- Scalp, Massive Fibroma of the, 154
- SCHILDT, PAUL Communications between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34
- SEEFELD, PHILIP H The Spread of Carcinoma

of the Rectum Invasion of Lymphatics, Veins and Nerves, 76

SELIGMAN, ARNOLD M Traumatic Shock, 238

Serum Amylase Test, use in Acute Trauma to the Pancreas, 594, and Plasma in the Replacement Therapy of Fatal Shock due to Repeated Hemorrhage, Amino Acids, 225

SHAFIROFF, B The Coagulability of Venous Blood of Normal and Diseased Legs, 482, Protein Metabolism and Bed Sores, 1015

SHIDLER, FREDERIC P Anterior Sacral Meningocele, 913

Shock Due to Repeated Hemorrhage, Amino Acids, Serum and Plasma in the Replacement Therapy of Fatal, 225, Further Experiences with the use of Adrenal Cortical Extract in Burn, 982, Immediate Effects on Renal Function of the Onset of, due to Partially Occluding Limb Tourniquets, 871, Particular Reference to Experimental Hemorrhage and Burn Gelatin as a Plasma Substitute, 193, Traumatic, 238

SHUTE, FRANK C Pilonidal Cysts and Sinuses, 706

SIDWELL, ALBERT E, JR Hydrocarbon Content of Nonboilable Surgical Gut Tubing Fluids, 285

Sinuses, and Pilonidal Cysts, 706

Sinus, Pilonidal, 430

Skin Removal in Radical Breast Amputation, 694

SMITH, FREDERICK Planned Timing in the Treatment of Wounds and Infections by means of Infrequent Occlusive Dressings, 921

SMITH, THOMAS E Pilonidal Cysts and Sinuses, 706

Sores, Protein Metabolism and Bed, 1015

SOUTHWORTH JAMES L Continuous Caudal Analgesia in Surgery 945

Spinal Anesthesia Advances in, 971

Spontaneous Rupture of Liver complicating Pregnancy, 396

Spread of Carcinoma of the Rectum Invasion of Lymphatics Veins and Nerves, 76

Stab Wound of the Heart, 46

STANTON, EUGENE Communications Between the Coronary Arteries Produced by the Application of Inflammatory Agents to the Surface of the Heart, 34

STEFKO, PAUL Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, 499

Sternum, A Method of Fixation for Fractures of the, 158

Stomach, Effects of Pedicle Grafts of Jejunum in the Wall of the, on Gastric Secretion, 499

STOUT, A P Carcinoma of the Breast, II—Criteria of Operability, 859, (continued), 1032, Hemangio Endothelioma A Tumor of Blood Vessels Featuring Vascular Endothelial Cells, 445

Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, 171

Subclavian Aneurysm Cured by Cellophane Imbibrosis, 478

Sulfonamides with and without Heparin, Experimental Studies on Peritoneal Adhesions, Fourth Report, 612

Surface Treatment of Burns, 761

Surgery, Continuous Caudal Analgesia in, 945, of the Pancreas, Some Physiologic Problems in, 576

Surgical Gut (Catgut) Tubing Fluid as a Tissue Irritant, 269, Management of Solitary Cysts, or Cystlike Structures, of Pulmonary Origin, 50, Principles Opposed to "Rule of Thumb" in the Treatment of Compound Fractures, 305, Treatment of Malignant Lymphoma, 1064

SUTTON, JOHN E Acute Postoperative Necrosis of the Liver, 149

SWARTLEY, WILLIAM B Choledochus Cyst, 91

SWEET, RICHARD H Total Gastrectomy by the Transthoracic Approach, 816

Synovial Cysts of the Popliteal Space Clinical Significance and Treatment, 438

T

Tannic Acid, Animal Experiments with, 417

TAYLOR, F H L Problems of Protein Nutrition in Burned Patients, 215

TAYLOR, R D Immediate Effects on Renal Function of the onset of Shock due to Partially Occluding Limb Tourniquets, 871

Therapy of Fatal Shock Due to Repeated Hemorrhage, Amino Acids, Serum and Plasma in the Replacement, 225

Thermal Burns, Basic Principles in the Treatment of, 187

Thoracic Aorta, Traumatic Rupture of the, 1071

Thrombin, use of, on Soluble Cellulose in Neurosurgery, 127

Thrombosis and Embolism, 728

Thyrocardiac Disease, 681

Tissue Irritant, Surgical Gut (Catgut) Tubing Fluid as a, 269

Tissue in Partial Lobectomy, Conservation of Lung, 353

Tissue Reactions Observed With Surgical Gut (Catgut), Irritant Properties of Tubing Fluids as a Factor in the, 288

TOCANTINS, LEANDRO M Review of Hemorrhagic Diseases and the Physiology of Hemostasis, 487

Total Gastrectomy by the Transthoracic Approach, 816

Tourniquets, Partially Occluding Limb, Immediate Effects on Renal Function of the onset of Shock due to, 871

Transactions of the American Surgical Association, 161

Transthoracic Approach, Total Gastrectomy by the, 816

Trauma to the Pancreas, Recognition and Management of Acute With Particular Reference to the use of the Serum Amylase Test, 594

Traumatic Rupture of the Thoracic Aorta, 1071

Traumatic Shock, 238

Treatment of Malignant Lymphoma, Surgical, 1064, of Myocardial Ischemia, Principles Underlying the Operative Approach to the, 788, of Surface of Burns, 761, of Wounds and Infections, Planned Timing in the by means of Infrequent Occlusive Dressings 921

- TREMBLAY, R G Primary Osteogenic Sarcoma of the Bladder, 887
Tubing Fluids as a Factor in the Tissue Reactions Observed with Surgical Gut (Catgut) Irritant Properties of, 288
Tubing Fluids, Hydrocarbon Content of Nonboilable Surgical Gut, 285
Tumor of Blood Vessels Featuring Vascular Endothelial Cells, Hemangio Endothelioma, 445
Tumors, Metastasizing Intracranial, 343
TISON, M DAWSON The Surgical Management of Solitary Cysts, or Cyst like Structures, of Pulmonary Origin, 50

U

- Ulcer The Effect on Gastric Acidity of Gastroenterostomy and Gastric Resection for Peptic 551, the Peptic, and Chronic Gastritis, 1005
Ulcers among Naval Personnel, Management of, 489
Upper Extremity and Pupil, Sympathetic Nerves to, 647
Use of One Flap to Restore Extensive Losses of the Middle Third of the Face 988
Use of Thrombin on Soluble Cellulose in Neurosurgery, 127

V

- VARS, H M Gelatin as a Plasma Substitute With Particular Reference to Experimental Hemorrhage and Burn Shock, 193
Vascular Endothelial Cells, A Tumor of Blood Vessels Featuring, Hemangio Endothelioma 445

- Veins, Nerves, and Lymphatics, Invasion of the, in the Spread of Carcinoma of the Rectum, 76
Venography, 469
Venous Blood of Normal and Diseased Legs, The Coagulability of, 482, Hemangioma of Skeletal Muscle, 465
VINCI, V Protein Metabolism and Bed Sores, 1015

W

- WALTERS WALTMAN Management of Ulcers among Naval Personnel, 489
WARD, WILLIAM C, 1st Lt Gunshot Wounds of the Abdomen, 780
WAUGH, JOHN M Nonmeckelian Diverticula of the Jejunum and Ileum, 377
WHIPPLE, ALLEN O Basic Principles in the Treatment of Thermal Burns, 187
WHITT, JAMES C Changes in Brain Volume and Blood Content after Experimental Concussion, 619
WOLFF, WILLIAM A Further Experiences with the use of Adrenal Cortical Extract in Burn Shock, 982
Wound of the Heart, Stab, 46
Wounds, Compound Fractures and Burns, the Study of the Prevention of Infection in Contaminated Fractures and, 171, Gunshot of the Abdomen, 780, of the Head, Experiences with Battle, 1, and Infections, Planned Timing in the Treatment of, by means of Infrequent Occlusive Dressings, 921
WRIGHT, A M Protein Metabolism and Bed Sores, 1015

